



# Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis

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Allergic rhinitis (AR) is a global health problem that causes major illnesses and disabilities worldwide. Epidemiologic studies have demonstrated that the prevalence of AR has increased progressively over the last few decades in more developed countries and currently affects up to 40% of the population worldwide. Likewise, a rising trend of AR has also been observed over the last 2-3 decades in developing countries including China, with the prevalence of AR varying widely in these countries. A survey of self-reported AR over a 6-year period in the general Chinese adult population reported that the standardized prevalence of adult AR increased from 11.1% in 2005 to 17.6% in 2011. An increasing number of original articles and

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clinical trials on the epidemiology, pathophysiologic mechanisms, diagnosis, management and comorbidities of AR in Chinese subjects have been published in international peer-reviewed journals over the past 2 decades, and substantially added to our understanding of this disease as a global problem. Although guidelines for the diagnosis and treatment of AR in Chinese subjects have also been published, they have not been translated into English and therefore not generally accessible for reference to non-Chinese speaking international medical communities. Moreover, methods for the diagnosis and treatment of AR in China have not been standardized entirely and some patients are still treated according to regional preferences. Thus, the present guidelines have been developed by the Chinese Society of Allergy to be accessible to both national and international medical communities involved in the management of AR patients. These guidelines have been prepared in line with existing international guidelines to provide evidence-based recommendations for the diagnosis and management of AR in China.

**Key Words:** Allergic rhinitis; China; diagnosis; treatment

## 1. INTRODUCTION

### 1.1 Chinese Guideline for allergic rhinitis (AR) workshop

To date, several international guidelines are available for the diagnosis and treatment of AR, in different parts of the world.<sup>1-9</sup> Of these, 7 have been written by specialist groups from Europe, UK, USA, Canada, Japan and Australia for the management of AR patients from the respective countries, whereas 2 guidelines—Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines and the World Allergy Organization (WAO) White Book on Allergy: Update 2013 ([www.worldallergy.org](http://www.worldallergy.org))—have been prepared as evidence-based documents in consultation with experts from all over the world.

Compared to the published international AR guidelines, the criteria for the diagnosis and therapeutic evaluation of AR in China were established by specialist groups and organized by the Editorial Board of the *Chinese Journal of Otorhinolaryngology* early in 1990. In view of the rapid growth of the prevalence and misconceptions of AR during clinical practice, these guidelines were subsequently updated by Chinese Guideline for AR workshops held in Haikou in 1997, in Lanzhou in 2004, in Wuyishan in 2009<sup>10</sup> and in Tianjin in 2015.<sup>11</sup> Moreover, a clinical practice for children with AR was developed by a group of specialists at a workshop held in Chongqing in 2012.<sup>12</sup> However, these Chinese guidelines for AR have been published mostly in Mandarin Chinese in the *Chinese Journal of Otorhinolaryngology Head Neck Surgery*. In view of the large number of original articles as well as well-controlled clinical trials of Chinese AR patients that have been published in many peer-reviewed international journals by Chinese researchers and authors over the past 2 decades, our knowledge and understanding of the epidemiology, pathophysiologic mechanisms, diagnosis, management and comorbidities of AR have been broadened substantially. Consequently, the Chinese Society of Allergy organized a workshop of the experts working in the different fields of AR management in China to develop the most updated Chinese Guidelines for the diagnosis and treatment of AR, using evidence-based models, as has been the case in the development of the ARIA international guidelines. Importantly, these

guidelines have also been developed in English in order that they can be readily accessed for reference by the non-Chinese speaking international fraternity.

### 1.2 Traditional Chinese Medicine

AR belongs to the category of ‘Bi Qiu’ in Traditional Chinese Medicine (TCM). ‘Bi Qiu’ refers to the disease which is characterised by sudden nasal itching, sneezing, rhinorrhea and nasal blockage. Thus, AR, vasomotor rhinitis and other similar diseases are all included in the ‘Bi Qiu’ category.

In ancient Chinese literature, the word ‘Bi Qiu’ was first found in the book of ‘Huangdi Neijing’ (Western Han Dynasty, 99 B.C.-26 B.C.). ‘Bi Qiu’ had several alternative terms such as ‘Qiu’, ‘Ti’, ‘Qiu Bi’ and ‘Runny nose’ and the record of the disease can be dated back to the book of ‘Rites’ (Western Han Dynasty, about 100 B.C.). The article of ‘Yue Ling’ in ‘Rites’ documented that “*In the last month of autumn, if the summer practices were observed, there would be great floods in the states. Then the winter stores would be affected and there would be many patients with sneezing and runny nose*”; thus indicating that the ancient Chinese people recognized the existence of a close relationship between AR and natural environment/climate events. Indeed, the ancient physicians believed that the main pathophysiology of AR was the dysfunction of ‘Zang-Fu’, including the lungs, spleen and/or kidneys, in addition to external pathogenic factors like Wind-Evil, Cold-Evil, or other unusual pathogens. Although several ancient TCM literature has discussed AR from different aspects, ‘Su Wen’ in ‘Huangdi Neijing’ suggested that “*(kidney) Deficiency would result in dysfunction of 9 orifices, and deficiency in the upper part and excess in the lower part of the body would manifest as runny nose and incessant lacrimation*.” ‘Tai Ping Sheng Hui Fang’ (Song Dynasty, 992 A.D.) suggested that “*the lung had its specific opening in the nose. When lung Cold affected nose ascending meridian, the runny nose would happen. Thus, the cause of AR was Deficiency, Excess, Cold or Heat, involving the ‘Zang-Fu’, organs of the lungs, spleen and/or kidneys*.”

While Western medicine was introduced into China about a century ago and has flourished since then, TCM has existed for almost all of China’s 5,000-year history and still plays an impor-

tant role in the Chinese medical system. TCM employs several treatment approaches in the management of AR including Chinese herbs taken orally or applied externally, acupuncture and the 'Daoyin (an ancient body-mind exercise aimed at health care as well as physical and spiritual purification)'. Each treatment can be used either alone or in combination, and generally complies with the theory of 'where there is a syndrome, there is a treatment' suggesting that different therapies and measures should be used according to the disease characteristics of the patient. Indeed, to date a large number of clinical studies have confirmed the effectiveness and safety of TCM in the treatment of AR.

### 1.3 Need for Chinese Guidelines for AR and their update

An ever increasing number of original articles and clinical trials have been published in peer-reviewed journals by Chinese researchers over the past 2 decades. This has substantially broadened our knowledge and database on the epidemiology, mechanisms, diagnoses, managements and comorbidities of AR, especially in Chinese subjects. Thus, in order to disseminate this knowledge and promote further research and clinical practice on the management of AR in China, the executive/organizing committee of the Chinese Society of Allergy decided that it was necessary to extensively review and summarize current literature, using an evidence-based model. Furthermore, it was also necessary to review the characteristics and current practice of clinical diagnosis and treatment of AR in China. Although Chinese guidelines for AR have been in existence since 1991 and subsequently updated several times, none of them have been published in English in any international peer-reviewed journal. Consensus among the Chinese professionals and practitioners indicated that the Chinese guidelines for AR had to be published in English from a Chinese viewpoint on the disease to be communicated to the international professionals and practitioners involved in the treatment of AR.

It is appreciated that since the recommendations in the Chinese guidelines were originally proposed by attendees at a workshop, these guidelines need to be validated and revised by both Chinese and international experts from all over the world. It is anticipated that the Chinese guidelines for AR published in English will serve as a reference for the treatment of AR by physicians, healthcare professionals and organizations involved in the treatment of AR in China and facilitate the development of relevant local standard of care documents for patients. Additionally, the guidelines will be updated every 2 years, adding relevant data and information from newly published papers in peer-reviewed journals and thus developing the guideline into a state-of-the-art document for specialists as well as for the general practitioner and other healthcare professionals. Consequently, it is expected that this document will encourage researchers and professionals to submit and publish their research in relevant peer-reviewed journals as well as update their knowledge of AR. Overall, the aim of this document is to provide an evi-

dence-based document on the diagnosis and management of AR across China, using a stepwise approach in line with other AR treatment guidelines.

## 2. EPIDEMIOLOGY

### 2.1 Global prevalence

Epidemiologic studies have revealed that the prevalence of AR has increased progressively in more-developed countries and currently affects up to 40% of the population worldwide.<sup>13,14</sup> A high prevalence of AR has also been recorded in the developed nations of the Northern Hemisphere, with 23%-30% of the population affected in Europe<sup>15,16</sup> and 12%-30% in the US.<sup>17</sup> The great diversity of AR prevalence is found in the non-Western populations of the Southern Hemisphere, with wide inter- and intraregional variations ranging from 2.9% to 54.1% between countries.<sup>18</sup> The global rising trend of AR has been observed in the past few decades and the AR prevalence has varied widely particularly in developing nations.<sup>2</sup> The increase in AR prevalence has been linked with increased urbanization and improvements in living standards, which have contributed to increased exposure to a variety of indoor and outdoor pollutants and allergens, the potentiating effects of which cannot be ignored on respiratory disorders. Although the prevalence and possible factors responsible for the etiologies of AR have been well documented in many developed countries, there is comparatively little information available for developing countries.<sup>19</sup> Large-scale coordinated studies specifically designed to estimate the prevalence of AR in regions with different environmental factors and climates are also required.

### 2.2 Previous AR prevalence in China

AR is one of the most common allergic disorders globally and affects 10% to 40% of the world's population.<sup>7</sup> While the majority of epidemiologic data come from surveys of AR prevalence conducted mainly in Europe and North America, and to a lesser extent in the developed Asian countries, relatively little epidemiologic data are available on AR prevalence in especially adults in China. One nationwide population-based study has assessed self-reported AR using validated questionnaire-based telephone interviews in over 38,000 adult in 11 major cities across China.<sup>20</sup> The interviews were conducted from September 2004 to May 2005 and the authors demonstrated that the prevalence of AR was highly variable, ranging from 8.7% in Beijing in North China to 24.1% in Urumqi in Northwest China. Compared to adults, however, more data are available from studies investigating the prevalence of AR in children in China. The majority of such studies have investigated the prevalence of AR in combination with asthma and eczema using the standardized and appropriately translated versions of the International Study of Asthma and Allergies in Childhood (ISAAC) protocols,<sup>21-23</sup> with only 1 nationwide study reporting the prevalence of specifically

AR in children in China.<sup>24</sup> In this study, a total of 23,791 children aged 6-13 years in 8 metropolitan capital cities of provinces in 4 regions were surveyed between November and December of 2005, using a cluster-stratified sampling method. The study demonstrated that the mean prevalence of childhood AR was 9.8% and ranged from 3.9% in Xi'an in Central China to 16.8% in Guangzhou in South China. The published data on the prevalence of AR in children and adults in China suggest that industrialization and the gross output of industries in most of the developed cities may reflect the prevalence of AR in certain cities in China. Moreover, these studies are limited due to nonuniform standardized study methods and diagnosis systems, which lead to biased comparisons among the studies.<sup>25</sup>

### 2.3 Current AR prevalence and trends

Compared to availability of progressive data for AR prevalence in many countries all over the world, there are insufficient comparable epidemiologic data for AR in China. As one of the largest countries in the world with a population of around 1.3 billion citizens, China has different topographic, climatic and economic conditions, which influence the lifestyle and exposure to allergens in different regions across the country. Thus, while the epidemiologic changes in AR prevalence is not unexpected due to the topographical and climatic conditions, the transition in socioeconomic status of many regions and individuals, particularly as a consequence of rapid urbanization and changes to a Western lifestyle over the past few years, appears to have further influenced the prevalence of AR. The influence of rapid urbanization and changes to a Western lifestyle has often impacted AR prevalence adversely in China as in the developed Western countries. However, a more comprehensive study involving subjects from 18 major cities in China has recently reported that there was an overall increase in the prevalence of self-reported AR in the general Chinese adult population during a 6-year period spanning from 2005 to 2011.<sup>26</sup> Compared to the national survey in 2005, the standardized prevalence of adult AR in the 18 major cities was 17.6% in 2011, with the highest prevalence of 23% recorded in Shanghai and the lowest prevalence of 9.8% recorded in Chengdu. These findings suggest that the prevalence of AR in China has not yet reached a plateau (Fig. 1). Other recent studies have focused on the prevalence of AR in almost 800 million people living in the rural areas of China. One study demonstrated that in North China while the prevalence of adult self-reported AR was significantly higher in the rural area than in the urban area (19.1% vs 13.5%), the prevalence of confirmable AR in these areas were 6.2% and 7.2%, respectively.<sup>27</sup> For preschool children, the prevalence of clinical AR in Beijing was found to be 19.5% in the urban areas and 10.8% in the rural areas.<sup>28</sup> However, these studies indicate that the limited availability of local health services and the unmet need for the diagnosis and therapy of AR in rural areas of China should be given greater consideration in the future. A multicenter in-

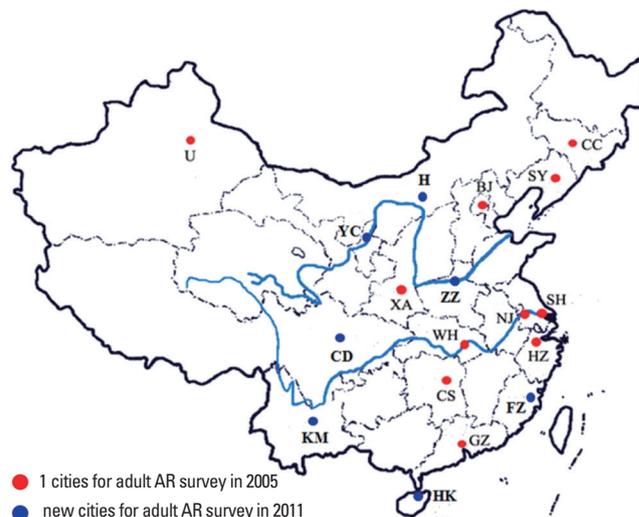


Fig. 1. Prevalence of adult AR in major cities in China in 2005 and 2011.

vestigation has evaluated the clinical features of 11,004 AR patients from 13 allergy centers in Central China.<sup>29</sup> The study showed that 9.7% of all patients had intermittent mild AR, 3.1% persistent mild AR, 33.9% intermittent moderate-severe AR, and 53.3% persistent moderate-severe AR. Furthermore, 61.6% and 42.2% of the patients had concomitant ocular and lower respiratory symptoms, respectively.<sup>29</sup> Collectively, these studies illustrate that AR is both a common and a growing national concern in China. They further indicate that future epidemiologic studies of AR in China performed at the national level should aim to assess the true prevalence of AR as demonstrated by a clinical diagnosis of AR confirmed by allergen-related examinations and employing standardized methodology across all centers involved in the study.

### 2.4 Comorbidities and complications

#### 2.4.1 Bronchial asthma

AR is an independent risk factor for the onset of asthma, and 40% of AR patients have or will have asthma.<sup>30</sup> As the upper and lower airway inflammatory responses are similar and interconnected in these individuals, this could be described as “one airway, one disease.” For AR patients, diagnosis for the coexisting asthma should be based on the patient’s medical history, symptoms and lung function examination. Indeed, the 2004-2005 survey of AR patients in the 11 major cities in China showed that among all the subjects with self-reported AR, an average of 9.2% suffered from asthma<sup>31</sup>: Beijing (12.7%), Changchun (8.3%), Changsha (7.5%), Guangzhou (5.4%), Hangzhou (13.1%), Nanjing (9.2%), Shanghai (9.3%), Shenyang (8.8%), Urumqi (6.3%), Wuhan (4.3%) and Xi’an (9.6%). Similarly, in 2011, a survey consisting of total 47,216 telephone interviews showed that the prevalence of asthma in the AR subpopulation was 28% (23).

#### 2.4.2 Allergic conjunctivitis

Itchy/watery eyes, redness and other eye symptoms are the main symptom of AR patients with allergic conjunctivitis, especially seasonal AR patients, whose incidence could be as high as 85%.<sup>32</sup> The AR survey during the year 2005-2011 showed that the incidence of eye symptoms in AR patients was 32%-59% based on medical history and clinical manifestation.<sup>26</sup> It is not difficult to diagnose allergic conjunctivitis, but differential diagnosis for other common conjunctival lesions should be noticed.

#### 2.4.3 Chronic rhinosinusitis

Allergic inflammation is a major factor related to chronic rhinosinusitis (CRS).<sup>33</sup> The cross-sectional survey of 7 cities in China recently showed the prevalence of CRS ranging from 4.8% to 9.7%.<sup>34</sup> Moreover, the prevalence of CRS was found to be 30% in AR patients and 23% in asthmatic patients, compared to just 6% and 7%, respectively, in subjects without AR or asthma. Similarly, larger surveys of subjects with self-reported AR from 11 and 18 major cities across China have demonstrated 13.3%<sup>31</sup> and 10.1%, respectively, of the AR patients<sup>26</sup> to have CRS. In another study, among all the 1,411 participants over 15 years old, 118 (8.4%) had self-reported CRS; patients with CRS had an increased prevalence of AR and chronic obstructive pulmonary disease compared to those without.<sup>35</sup> Furthermore, the quality of life was significantly impaired in patients with CRS than in those without, with the quality of sleep being markedly impaired in CRS patients. Although this study did not assess the correlation between CRS severity and impairment of sleep, it is possible that the impairment in CRS patients with AR may indeed be correlated with the severity of CRS as shown in patients with AR.

#### 2.4.4 Upper airway cough syndrome

AR and sinusitis are a common cause of chronic cough in children and adults.<sup>12,36</sup> Nasal secretions reflux from the nose and the throat directly or indirectly stimulate cough. Cough resulting from chronic sinusitis may thus be the main clinical manifestation of upper airway cough syndrome (UACS). A pilot study of 393 children with cough as a chief complaint in Chengdu has recently shown that 45.8% of the children suffered from AR. Similarly, a multicenter survey investigating causes of chronic cough in China found that UACS was most frequently associated with AR (63.4%).<sup>37</sup>

#### 2.4.5 Otitis media

Secretory otitis media (SOM) is a nonsuppurative inflammatory disease. Middle ear effusion—which includes serous fluid and pulp-like mucus—and hearing loss are the main features, and AR is regarded as one of the possible risk factors inducing SOM in children.<sup>12</sup> Indeed, one study from the UK found that the prevalence of AR in patients with chronic or recurrent OME ranged from 24% to 89%.<sup>38</sup> Similarly, a study from Qingdao city in China has indicated that children with SOM have increased

annual frequency of AR.

### 3. MAJOR ALLERGENS IN CHINA

#### 3.1 China in general

Exposure to inhalant allergens is the primary inducer of AR symptoms; with particularly the aeroallergens, which include both outdoor and indoor allergens, being the most common allergens. Outdoor allergens, which mainly include pollen and fungi, are positively associated with the development of seasonal/intermittent AR, whereas indoor allergens, which typically include mites, animal dander, cockroach and fungi, are the major cause of perennial/persistent AR. Although exposure to certain occupational allergens may also lead to AR, exposure to food allergens rarely causes isolated nasal allergy symptoms.<sup>7,11</sup> Due to the effect of geographic, climatic and humanistic factors, the types of allergens inducing AR vary significantly among regions. Identifying major local allergens is thus the first step to AR management involving diagnosis, prevention and allergen-specific immunotherapy (AIT).

In 1964, Voorhorst<sup>39</sup> discovered that the allergenic properties of house dust originated from the component of mites. The first mite allergen was isolated by Fain in 1966 from the genus *Dermatophagoides pteronyssinus* (*Der p*), and since then more species of mites have been discovered.<sup>40,41</sup> In China, Chan and colleagues<sup>42</sup> have contributed greatly to the identification of diverse *Dermatophagoides farina* (*Der f*) allergens by proteomics. The novel allergens from *Der f* such as *Der f* 25 (triosephosphate isomerase), *Der f* 26 (myosin alkali light chain), *Der f* 27 (serpin), *Der f* 28 (heat shock protein), *Der f* 29 (cyclophilin), *Der f* 30 (ferritin), *Der f* 31 (cofilin), *Der f* 32 (pyrophosphate) and *Der f* 33 (alpha-tubulin) have greatly extended the spectrum of dust mite allergens,<sup>43</sup> and the findings from Liu and colleagues<sup>61</sup> could be of benefit for the guidance on more effective diagnosis and AIT of HDM respiratory allergy in China.

Pollen is a common aeroallergen worldwide. Ragweed allergen was described by Carl Linnaeus in the 18th century,<sup>44</sup> but since then more highly allergenic pollen inducing seasonal allergic symptoms in respiratory tract have been discovered all over the world including China. In the 1950s, it was first reported that the genus *Artemisia* was the most important source of allergenic pollen in North China.<sup>45</sup> Many new pollen allergens have subsequently been described in China. Indeed, during the mid-1980s to early 1990s, nearly 80 provincial- and municipal-level hospitals participated in a national epidemic survey on anemophilous allergenic pollen, resulting in the publication of a book entitled “*A National Survey of Airborne and Allergenic Pollen in China*” in 1991. This book summarizes the geographical distribution and drift patterns of airborne allergenic pollen by regions in mainland China and is designed for reference by clinicians involved in the treatment of allergic disease. It is worth noting that increasing urbanization and alien plant invasion

have led to emergence of different trends in diffusion of pollen allergen.

### 3.2 Current data and trends

Zhang and colleagues<sup>25</sup> reviewed the pattern of sensitization to inhalant allergens among AR patients in mainland China and found that the prevalence and type of aeroallergens were different among various cities and regions. A survey by Li and colleagues<sup>46</sup> of 6,304 patients suffering from asthma and/or rhinitis in 17 cities from 4 regions of China showed that the overall prevalence of positive skin prick responses was highest for *Der f* (59.0%), *Der p* (57.6%), and *Blomia tropicalis* (40.7%), and lowest for mixed mould IV (4.4%), mixed grass pollen (3.5%), and mixed tree pollen (2.2%). The prevalence of sensitization to other allergens ranged from 16.1% for American cockroach, 14.0% for dog, 11.5% for *Blattella germanica*, 11.3% for *Artemisia vulgaris*, 10.3% for cat, 6.5% for *Ambrosia artemisiifolia*, and 6.3%

for mixed mould I.<sup>46</sup> Moreover, this study showed that the prevalence of sensitization to allergens were different between adults and children, with *Der p* and *Der f* reported as the predominant aeroallergens in perennial/persistent AR individuals in China. The prevalence of positive skin prick test results to *Der p* in Qingdao, Zhengzhou, Xiamen, and Guangzhou have been reported to be 69.6% (66.4%), 86.32% (87.54%), 76.56% (77.16%), and 72.84% (76.36%), respectively.<sup>47</sup> We still reviewed 146 published reports documenting the prevalence of sensitization to *Der p* and *Der f* among 89,779 AR patients from 7 major regions across China, and drafted a nationwide epidemiologic map to better represent the patterns of sensitization to *Der p* and *Der f* in these regions (Fig. 2). This map indicated that overall sensitization to the 2 allergens is fairly similar, although the order of regional distribution for positive sensitization rates was South > Central > East > Southwest > Northwest > Northeast > North. These data suggested an obvious geographic difference of the preva-

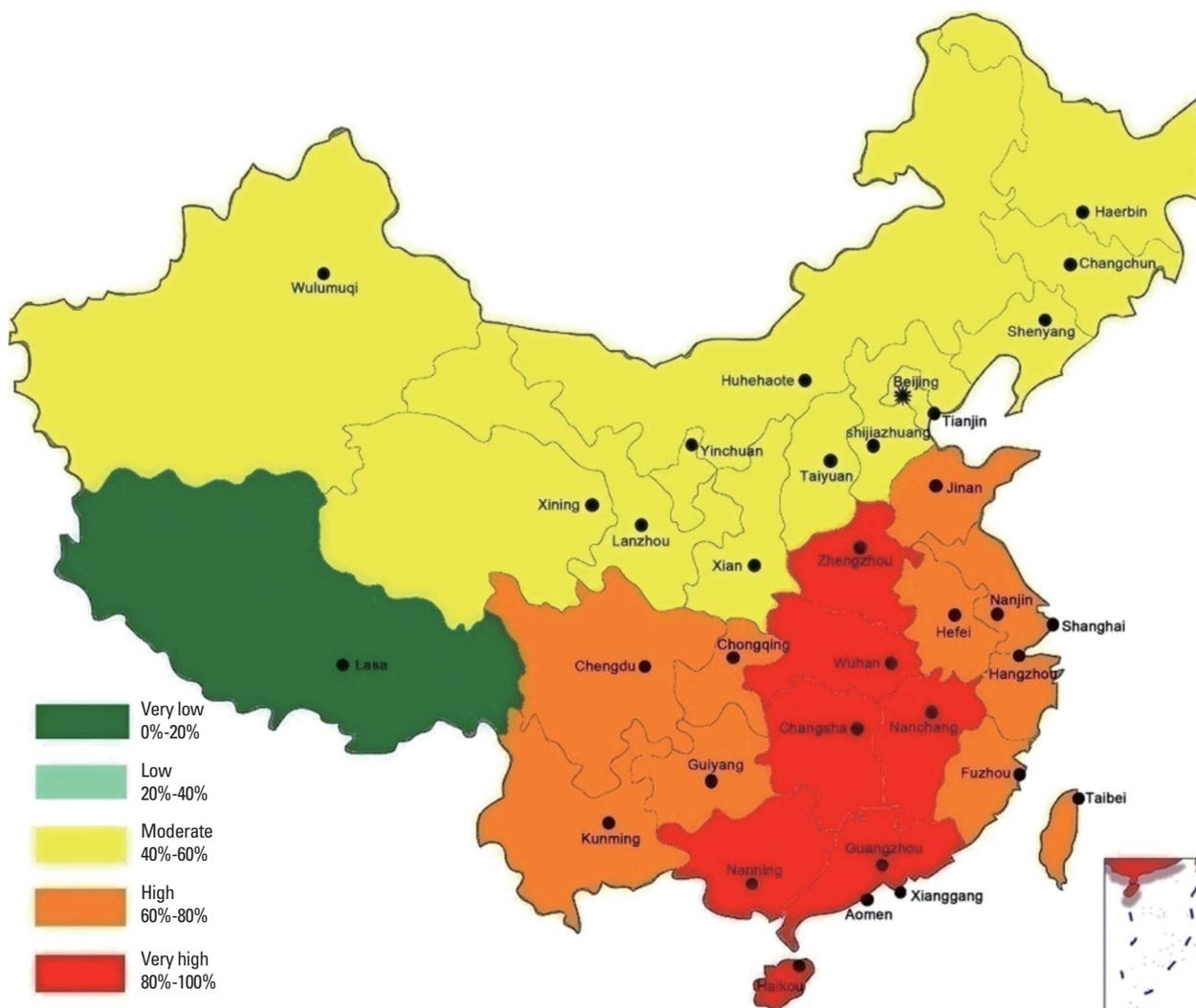


Fig. 2. The prevalence of sensitization to dust mites in China.

**Table 1.** The main airborne tree pollens in different regions of China

Region	Tree pollen genus
Northeast China	<i>Populus, Ulmus, Pinus, Salix, Birch, Acer, Quercus</i>
North China	<i>Populus, Platane, Pinus, Salix, Fraxinus, Birch, Ailantus</i>
Northwest China	<i>Populus, Ulmus, Salix, Acer, Cupressaceae, Platane, Corylus, Fraxinus</i>
East China	<i>Platane, Pinus, Cupressaceae, Broussonetia, Pterocarya Kunth, Ulmus, Salix, Populus</i>
Central China	<i>Platane, Cupressaceae, Pinus, Broussonetia, Pterocarya Kunth, Quercus, Ligustrum, Morus</i>
Southwest China	<i>Salix, Pinus, Alder, Cupressaceae, Broussonetia, Populus, Firmiana Marsili, Cryptomeria</i>
South China	<i>Pinus, Broussonetia, Eucalyptus, Cupressaceae, Casuarina, Morus, Juglans L, Palmae</i>

lence of sensitization to dust mites, demonstrating a trend of decrease from south and east to north and west in China. It is likely that the complicated geographic environment, climate, human activity, and air pollution contribute to these regional differences in the pattern of allergen sensitization. Nevertheless, an overall upward trend in the prevalence of sensitization to dust mites in China has been observed in recent decades, and this may be related to the rapid change towards a “Western lifestyle.”

Airborne pollen is the most frequent and seasonal cause of AR in the western and northern regions of China. The existence of a considerable regional difference in the distribution of pollen species and counts is due to the geographic and vegetation differences in China; thus *Artemisia* pollen is the most common allergenic one in the northern part of the Yangtze River (Beijing, Xinjiang, Shanxi, Shandong, Shenyang, Lanzhou, and Ningxia) in China. Tables 1, 2 show the geographic distribution of tree, grass, and atrazine pollen in different regions in China.<sup>48,49</sup> Thus, availability of this information and establishment of national real-time monitoring of atmospheric pollen may make the prevention and treatment of AR patients with pollen allergy and seasonal migration possible.

With improvements in living standards, pet ownership has become more prevalent in China. The number of domestic pets in China has increased 9-fold in 2013 compared to 2003. One survey showed that the positive serum sIgE rates of cat and dog allergens in AR child patients in Shanghai were 6.9% and 28.2%, respectively.<sup>50</sup> Wang and colleagues<sup>51</sup> conducted a 10-year retrospective study to investigate the trends in the prevalence of sensitization to common aeroallergens among AR patients in Guangzhou, the largest city in South China. The authors showed that the prevalence of sensitization to cat hair and dog dander had increased nearly 2-fold during the past decade, suggesting the importance of controlling the pet ownership and introducing SIT for pet allergy.<sup>51</sup>

**Table 2.** The main grass and atrazine pollens in different regions of China

Region	Grass and atrazine pollen genus
Northeast China	<i>Artemisia Annual, Humulus, Gramineae, Ambrosia, Chenopodiuml, Cyperaceae</i>
North China	<i>Artemisia Annual, Humulus, Gramineae, Chenopodiuml, Amaranthaceae, Ambrosia</i>
Northwest China	<i>Artemisia Annual, Chenopodiuml, Humulus, Gramineae, Helianthus, Amaranthaceae</i>
East China	<i>Artemisia Annual, Gramineae, Humulus, Ambrosia, Chenopodiuml, Amaranthaceae</i>
Central China	<i>Artemisia Annual, Gramineae, Humulus, Ambrosia, Chenopodiuml, Amaranthaceae</i>
South China	<i>Gramineae, Artemisia Annual, Chenopodiuml, Humulus, Amaranthaceae, Ricinus</i>
Southwest China	<i>Artemisia Annual, Gramineae, Chenopodiuml, Humulus, Helianthus, Ricinus</i>

## 4. BURDEN OF AR IN CHINA

### 4.1 Health economics

The direct and indirect costs associated with the management of AR are a huge burden on the society.<sup>52</sup> Data from the National Bureau of Statistics of China (<http://www.stats.gov.cn/>) indicate that there were 1.37 billion people in China at the end of 2014. A recent report showed that the standardized prevalence of self-reported AR is 17.6% in 18 major cities of China, and the prevalence of self-reported asthma 28% in the AR population.<sup>26</sup> From these data, it is estimated that 0.24 billion people could be affected by AR and of these 67.51 million people could have AR combined with asthma (ARS).

Although there is no report of the direct cost of AR in China to date, a study by Chen and colleagues<sup>53</sup> estimated that the direct cost of an ARS patient receiving subcutaneous immunotherapy (SCIT) or a specific medical treatment in Wuhan, China in 2013 was \$982 and \$259 per year, respectively. Since the income and economy of Wuhan represent the average levels of China, using the data of Chen and colleagues<sup>53</sup> it is possible to estimate that the total societal cost in China could be \$17.49 billion per year for all ARS patients if they received only medicinal therapy and no immunotherapy.

Furthermore, as the average disposable income of Wuhan was \$4,451 per person in 2013 (<http://www.whtj.gov.cn/>), it can be estimated that as the cost of SCIT is not included in most medical insurance, the patients would have to spend 22% of their disposable income for their treatment involving SCIT.

In addition to the direct costs, there are considerable indirect costs such as decreased work productivity, workdays (adults) or school days (children) absent due to illness.<sup>54</sup> Expenses managing the comorbidities of AR such as sinusitis, bronchitis and otitis media should also be considered “hidden” costs of AR.<sup>55</sup>

#### 4.2 Effects of AR on life quality

AR is an important and serious public health problem not just because of its high prevalence but also because it adversely impacts patients' quality of life (QOL) with respect to work productivity, school performance, social life, and mental and psychologic states. The disease burden comes from the morbidity of nasal symptoms, numerous comorbidities, and the impairment of multiple domains of QOL. Patients report that the disorder has a marked detrimental effect on their sleep, social life, and attendance and functioning at school and work,<sup>56</sup> and patients also experience other psychologic symptoms that include fatigue, mood changes, anxiety, and depression.<sup>57,58</sup> Yin and colleagues<sup>59</sup> found that symptoms of AR could cause great discomfort in the patient's daily functioning, including playing a satisfactory role in family, and professional and social life. Furthermore, nasal symptoms were significantly associated with anxiety, and emotion and behavior problems. A previous study on QOL of AR patients, using several instruments including the Medical Outcomes Study Short-Form 36-Item Health Survey (SF-36), Eysenck personality questionnaire (EPQ), self-rating anxiety scale (SAS) and self-rating depression scale (SDS), showed that the patients' health status declined in all domains, especially in general health perceptions, physical role functioning, and emotional role functioning.<sup>60</sup> Furthermore, although the patients had no obvious differences in personality characteristics, the tendency to develop anxiety, but not depressive emotion, was observed. A study by Liu and colleagues<sup>61</sup> using the Chinese version of SF-36 has also demonstrated pronounced decrements in general health, role-emotional, and role-physical dimensions in mild AR patients, whereas significant impairments were noted in all domains in patients with moderate to severe AR. In the latter group, the impairments were most pronounced in general health, role-emotional and social function domains. Similarly, in a more recent prospective cohort study of patients with moderate/severe AR, using visual analogue scale (VAS) and AR Control Test (ARCT) demonstrated impairments in sleep in 86.9%, work life in 84.9%, social activities in 81%, and physical activities in 90.1% of the patients.<sup>62</sup> Indeed, nasal symptoms including stuffy/blocked nose, runny nose, sneezing and post nasal drip, as well as the consequential practical problems, including inconvenience of having to carry tissues or handkerchief, need to rub nose/eyes, and need to blow the nose repeatedly, have been shown to be the most troublesome aspects of AR.<sup>63</sup> Li and colleagues<sup>64</sup> employed the rhinoconjunctivitis quality of life questionnaire (RQLQ) to assess the QOL in AR patients according to the sensitization profile for relevant aeroallergens in North China and showed that this was worse in patients sensitized to tree pollens or weed pollens than in those sensitized to HDMs. Although QOL of the patients was not significantly correlated with the level of specific IgE to the causative allergen, the QOL varied with the allergen responsible for symptoms.<sup>64</sup> A study using Symptom Checklist-90 (SCL-90) has shown the SCL-90 scores

to be significantly higher for the obsessive-compulsive, hostility, somatisation, and psychoticism dimensions in AR patients than in healthy controls.<sup>65</sup> This study further indicated that the psychologic status of AR patients worsens with comorbid asthma. However, the effect of gender is somewhat unclear. A study by Xi and colleagues<sup>65</sup> did not demonstrate effect of gender on SCL-90 scores of AR patients, whereas a study by Lv and colleagues<sup>66</sup> demonstrated poorer psychologic functioning in female patients with moderate-to-severe persistent AR than in nonallergic women. VAS and RQLQ have also been employed to assess symptom severity and QOL, respectively, in Chinese children with AR.<sup>67</sup> As for the adults, nasal symptoms were the most impairing aspect of QOL, with nasal itching and sneezing the main factors affecting the quality of sleep. While the quality of sleep may affect non-hay fever symptoms and emotions, rhinorrhea appeared to be the main factor causing embarrassment to the child. VAS was significantly correlated with RQLQ, and skin prick tests (SPTs) results correlated with both VAS and RQLQ, suggesting a close relationship between the allergen level and symptom severity/QOL.<sup>67</sup> Song and colleagues<sup>68</sup> investigated the effect of AR in 814 middle school students aged 10 to 17 years enrolled from 4 schools in Changsha city, using VAS, to assess the effect of AR on sleep, emotion, and memory of these students. The rates of students reporting a moderate-to-severe impact of AR symptoms on sleep, emotion, and memory were 47.14%, 14.29%, and 27.14%, respectively, compared to 21.96%, 6.83%, and 11.28%, respectively, for children without AR. The authors suggested that AR significantly decreased the sleep quality and memory of these students, while emotional issues were increased with the onset of AR.<sup>68</sup> AR has also been shown to impact on the sleep and attention in children and to decrease the QOL of children.<sup>68</sup> Similar to these findings in Chinese AR patients, the symptoms of AR have also been shown to impair the QOL of patients from diverse regions of the world by adversely impacting on sleep, daily activities, physical and mental status, and social functioning.<sup>69</sup> Poor sleep leads to fatigue and daytime somnolence, resulting in decreased performance, productivity, and social functioning as well as increased risk of associated diseases. A study from Europe has recently suggested that the severity of AR adversely impacts on patients' QOL to a greater degree than the duration of disease.<sup>70</sup> Effects of gender, marital status, residential area, and duration of symptoms have also been shown to significantly impact on the patient's well-being.<sup>71</sup> QOL of children with AR has been shown to be severely compromised due to frequent night awakenings, easy fatigue, defects of language, and irritability, which all have a negative influence on learning abilities. Indeed, AR may negatively impact on the QOL of the whole family because it could interfere with social life and financial costs.<sup>72</sup>

#### 4.3 Psychologic impact

Although AR is not life-threatening, the serious negative influ-

ence of the disease on the patient's quality of life and psychologic status has received more attention in recent years. Several studies have investigated the influence of psychosocial factors on atopic disorders and the effect of atopic disorders on mental health, demonstrating that there is a significant bidirectional relationship between psychosocial factors and future atopic disorders as well as between atopic disorders and future poor mental health.<sup>73</sup> Cuffel and colleagues<sup>74</sup> carried out a questionnaire survey of 85,298 people and reported that the incidences of anxiety and depression in AR patients were 1.41 and 1.7 times, respectively, that of the general population. Several studies have shown an association between the risk of suicide during the hay fever season and seasonal pollen counts.<sup>75,76</sup> Sansone and colleagues<sup>76</sup> reviewed the studies investigating the relationships between allergies and anxiety/mood syndrome and found that the majority of studies (9 of 11 studies on anxiety syndromes, and 10 of 12 studies on depressive syndromes) indicated associations between allergies and anxiety/mood syndromes. One population-based study has suggested that AR may even be a risk factor for suicide.<sup>77</sup> Similarly, some studies have investigated the psychologic effects of AR in Chinese subjects. Xi and colleagues<sup>65</sup> used the SCL-90 to study psychologic characteristics between AR patients and nonallergic individuals and demonstrated that there were significant differences between the 2 groups; with the SCL-90 scores for somatization, compulsion, interpersonal sensitivity, hostility, and psychosis being higher in the AR patients. In another study, Lv and colleagues<sup>61</sup> assessed the psychologic aspects of Chinese female outpatients with moderate-to-severe persistent AR and nonpsychometric adult females, using the Minnesota Multiphasic Personality Inventory (MMPI). The authors concluded that women with AR have poor psychologic functioning as indicated by poorer MMPI scores for hypochondriasis, depression, hysteria, psych asthenia, schizophrenia and social introversion. Moreover, the women with AR felt depressed and unhappy, and were more likely to be pessimistic about the future. Some exhibited apprehensive behavior, and even anger and resentment because they had likely experienced many hours in hospital and felt misunderstood by physicians as well as by family members or others, and had a greater tendency to be alone. Another study by these authors has indicated that the psychologic status of seasonal AR patients was likely to be influenced markedly by the symptoms of AR, such as nasal obstruction and nasal itching.<sup>78</sup> Collectively, these findings suggest that allergists should target both allergic diseases and subsequent psychologic disorders as a whole, rather than treat them as separate disease entities.

## 5. DEFINITION AND CLASSIFICATION

### 5.1 AR

AR is a symptomatic disorder of the nose, which is defined as an infectious inflammation associated with IgE-mediated in-

flammatory response to allergens. The symptoms of AR includes paroxysmal sneezing, rhinorrhea, nasal congestion and itchin.<sup>4,7,8,11,79</sup>

The classification of AR in China has been adjusted continually following a long period of research and discussion. According to the original classification in 1997, AR was divided into 2 categories: perennial (the onset of symptoms is all year round and symptoms last for at least 6 months per year) and seasonal (the onset of symptom is seasonal). In order to adapt to the situation in China, the classification was subsequently modified into 4 categories by combining the traditional classification with the classified standard recommended by ARIA in 2004: seasonal intermittent, seasonal persistent, perennial intermittent, and perennial persistent.<sup>80</sup> Furthermore, the severity of AR was classified as mild (the symptoms are not interfering with sleep, daily activities, physical exercise, entertainment, work and study) and moderate-severe (the symptoms are disturbing and severely affected patients' life mentioned above) in accordance with the ARIA classification. Thus, the classification was modified to being intermittent (<4 days/week or <4 weeks/year) or persistent ( $\geq 4$  days/week and  $\geq 4$  weeks/year) by the frequency of symptoms and to being mild (the symptoms are not interfering with quality of the patient's life) or moderate-severe (the symptoms cause severe impairments in quality of life of patients) according to the severity of symptoms.<sup>10</sup> More recently, the classification of AR has been further modified by the addition of the type of allergen in 2016.<sup>11</sup>

Taking the Chinese patients' situation and international common classification into consideration, AR can thus be classified in 3 ways as shown in Table 3.

- 1) The type of allergen
  - a) SAR: the onset of symptoms is seasonal. Aeroallergens (pollen and fungi) are the most common allergens.
  - b) Perennial AR: the onset of symptoms is year-round. The allergens include dust mites, animal dander, tree pollen, *etc.*
- 2) The frequency of symptoms<sup>4,10,11,80</sup>
  - a) Intermittent AR: <4 days/week or <4 weeks/year
  - b) Persistent AR:  $\geq 4$  days/week and  $\geq 4$  weeks/year
- 3) The severity of symptoms<sup>4,10,11,80</sup>

**Table 3.** Classification of AR

Type of allergen
i. Seasonal AR
ii. Perennial AR
Frequency of symptoms
i. Intermittent AR (<4 days/week or <4 weeks/year)
ii. Persistent AR ( $\geq 4$ days/week and $\geq 4$ weeks/year)
Severity of symptoms
i. Mild AR
ii. Moderate-severe AR

- a) Mild AR: the symptoms are not interfering with quality of the patient's lifestyle including daily life, work, study, etc.
- b) Moderate-severe AR: the symptoms cause severe trouble in quality of the patient's life.

As the duration of aeroallergen pollen season depends on climatic conditions and geographic location, in some areas where the aeroallergen pollen season is year-round, this causes difficulty in classifying AR by the type of allergen. Thus, in such areas AR is divided into the seasonal, perennial or the mixed (perennial with seasonal exacerbations) types.<sup>79</sup>

The classification of AR by the frequency of symptoms also has some limitations.<sup>4</sup> It is particularly difficult to sort out patients with perennial symptoms, but for less than 4 days/week (more like "persistent"), into "intermittent" AR type.

The appropriate classification of AR should thus take into consideration different geographic conditions and patients' situations, and needs to be continuously improved accordingly.

## 5.2 Local AR

Local AR (LAR) is a newly described form of AR. LAR patients have typical clinical symptoms of AR, but without classic systemic atopy.<sup>81</sup> In LAR patients, nasal symptoms, local sIgE production, and type 2 response-dominated inflammation in nasal mucosa can be induced during natural exposure to aeroallergens or by nasal provocation test (NPT).<sup>82</sup>

LAR affects about 47% of patients previously diagnosed as non-AR.<sup>81</sup> Key features for the differential diagnosis of LAR and AR are shown in Table 4. LAR shares similar clinical symptoms, including rhinorrhea, nasal obstruction and itching, sneezing, and associated ocular symptoms, with AR; however, SPT and serum sIgE are negative for LAR patients. On the contrary, similar to AR patients, NPT is able to induce positive immediate, late, and dual nasal symptoms accompanied by increased levels of sIgE, tryptase, and eosinophil cationic protein (ECP) in the nasal secretions of LAR patients.<sup>83</sup> NPT can be evaluated by assessing the change in nasal volume (NV) using acoustic rhinometry, and nasal symptoms can be score using a VAS system. A 30% increase in the total VAS plus a 30% decrease in the vol-

**Table 4.** Diagnosis of AR and LAR

	AR	LAR
Symptoms	Rhinorrhea, nasal obstruction, nasal itching, sneezing with or without ocular symptoms	Rhinorrhea, nasal obstruction, nasal itching, sneezing with or without ocular symptoms
Disease duration	Persistent or intermittent	Persistent or intermittent
Laboratory test	SPT and/or serum sIgE antibody positive	SPT and serum sIgE antibody negative
Aeroallergen nasal provocation test	Positive	Positive

ume of nasal cavity from 2 to 6 cm (NV 2-6 cm) is considered a positive response.<sup>84</sup> The release of ECP and tryptase is significantly up-regulated in the nasal secretion as early as 15 minutes after challenge and can last for 24 hours with a gradual increase. In some patients, sIgE can be detected in nasal secretion at baseline, and local sIgE levels can be further rapidly increased after NPT.<sup>85</sup> Due to the lack of standardized provocation reagents in China and the potential side effects of NPT, NPT is only carried out in a laboratory, and seldom in the clinic. Thus, the prevalence of LAR in China is not clear and this disease entity has not been widely recognized by Chinese physicians. Patients with LAR may present persistent or intermittent symptoms, with severity classified as mild, moderate or severe, similar to AR patients.<sup>81</sup> Indeed, a prospective follow-up study has recently shown that only a small number of individuals with LAR may evolve to typical AR with systemic atopy, suggesting that LAR is more likely a distinct entity.<sup>86</sup>

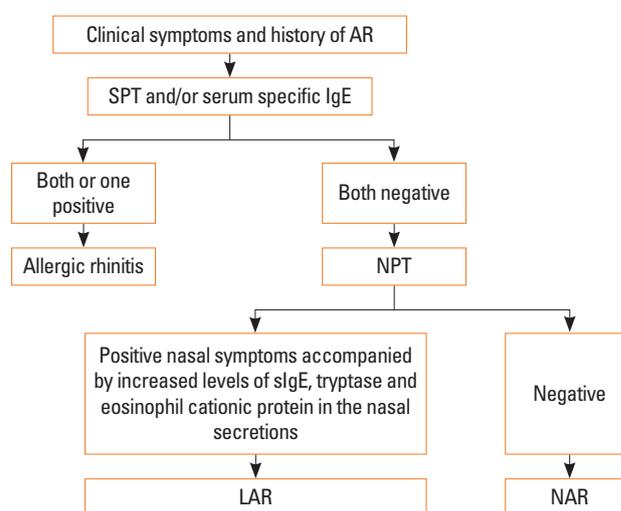
A diagnostic flowchart for LAR is summarized in Fig. 3.

## 6. MECHANISMS

### 6.1 Genetic factors

#### 6.1.1 Genetics

AR, like other allergic diseases, is an inflammatory disease with a complex genetic component in the etiology of AR. Based on the European studies of twins, it was estimated that AR exhibited a heritability ranging between 33% and 91%.<sup>87,88</sup> In China, a genetic epidemiologic study involving 23,825 families from Jiangsu province reported that the average AR heritability of the first, the second, and third generations was 81.86%.<sup>89</sup> Earlier studies using genome-wide linkage scans for AR in affected-sib-pair families from European and Japanese populations demonstrat-



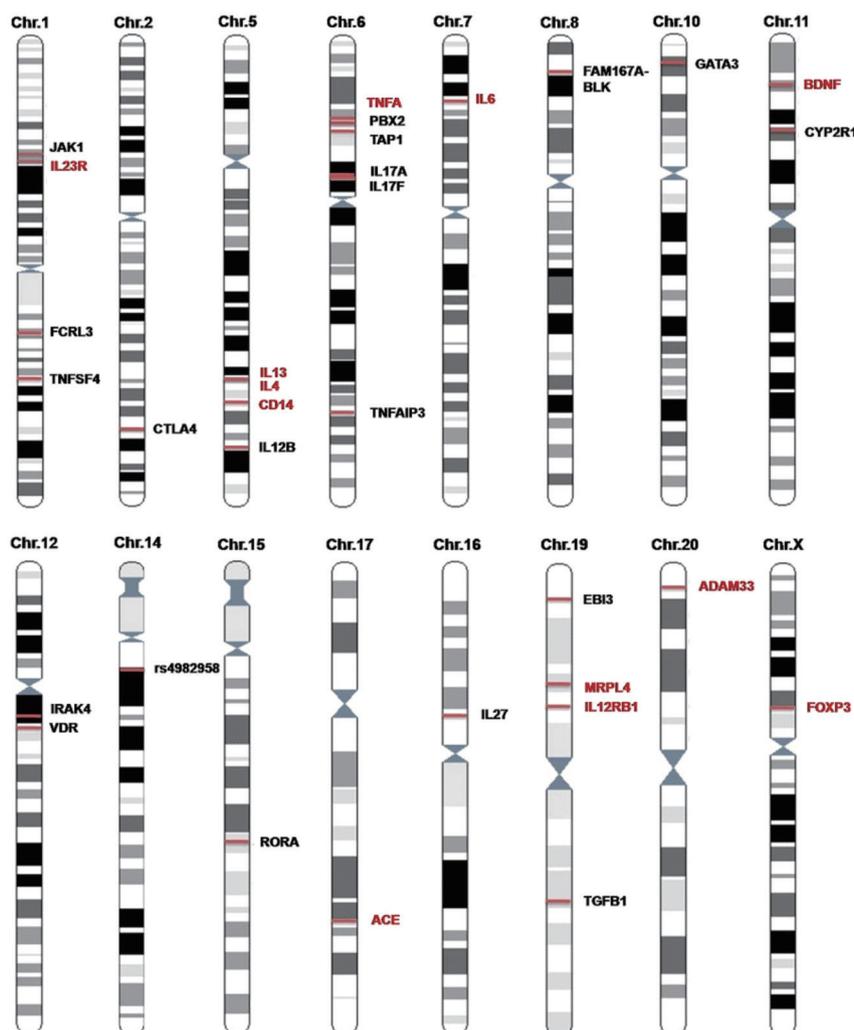
**Fig. 3.** Diagnostic flowchart for LAR. AR, allergic rhinitis; SPT, skin prick test; IgE, immunoglobulin E; NPT, nasal provocation test; LAR, local allergic rhinitis; NAR, non-allergic rhinitis; sIgE, serum-specific IgE.

ed that the chromosomes 1p31, 2q32, 3p24-p14, 4q32.2, and 9q22-q34 were likely to contain the candidate gene loci associated with the development of AR.<sup>90-92</sup>

With the rapid development of genotyping techniques, large population-based association strategies have been carried out more widely to investigate specific susceptibility genes for AR. Because of the important role in antigen presentation, the human leukocyte antigen (HLA) is known to be an important genetic susceptibility locus for a variety of allergic diseases. Moreover, several HLA alleles have been shown to be associated with AR in different ethnic groups. In an earlier study, Lin and colleagues<sup>93</sup> first investigated the association between several HLA alleles (HLA-B27, RR of A31, A28, B12, and A33) and the genetic susceptibility of AR in a Chinese population. Subsequently, several studies have been performed in different ethnic groups from different parts of China (northeastern area,<sup>94</sup> Beijing,<sup>95-97</sup> Xinjiang<sup>98</sup>) and demonstrated a strong association between HLA

class II alleles (DR and DQ) and AR. However, these studies have been limited by the complicated nature of the genotyping procedures employed and the small sample sizes (<100 AR patients) investigated. More recently, Zhao and colleagues<sup>99</sup> have employed polymerase chain reaction sequence-based typing (PCR-SBT), a form of higher resolution HLA typing, to assess the HLA-II gene alleles associated with AR in HDM-sensitive Han Chinese subjects and control subjects. The authors reported that HLA-DQB1\*06:01:01 and HLA-DRB1\*08:03:02 were significantly increased in HDM-sensitive AR patients compared to healthy controls, suggesting that these alleles may confer a risk of AR in Han Chinese subjects sensitized to HDM.

Candidate gene studies have also implicated a number of several other susceptibility genes related to AR in Chinese subpopulations (Fig. 4). These include cytokines (IL13,<sup>100,101</sup> IL4,<sup>102</sup> IL12B,<sup>103</sup> IL17A,<sup>103,104</sup> IL17E,<sup>102</sup> IL6,<sup>105</sup> IL27<sup>106</sup>) cytokine receptors (IL23R,<sup>107</sup> IL12RB1,<sup>108</sup> and EBI3<sup>109</sup>) immunity pathway molecules (JAK1,<sup>110</sup>



**Fig. 4.** Susceptibility loci of AR in Chinese population studies. Some loci were reported only in Chinese populations (loci shown in black) or in both Chinese populations and other ethnic populations (loci shown in red).

FCRL3,<sup>111</sup> TNFSF4,<sup>112</sup> CTLA4,<sup>113</sup> CD14,<sup>114</sup> TNFA,<sup>115</sup> PBX2,<sup>116</sup> TAP1,<sup>117</sup> TNFAIP3,<sup>118</sup> FAM167A-BLK,<sup>112</sup> GATA3,<sup>119</sup> IRAK4,<sup>120</sup> RORA,<sup>103</sup> TGFB1,<sup>121</sup> and FOXP3<sup>109</sup>), allergic airway inflammation and airway remodelling molecular genes (BDNF,<sup>122</sup> CYP2R1,<sup>123</sup> VDR,<sup>123</sup> ACE,<sup>124-126</sup> MRPL4,<sup>115</sup> ADAM33<sup>127,128</sup>), and others (rs4982958 at 14q11.2).<sup>129</sup> Fig. 4 shows that Chinese subpopulations and other ethnic groups, including white European, Koreans and Japanese, share a large number of these genetic susceptibility loci.

Loci on the chromosome 5q31-33 have been shown to be hotspots for AR susceptibility. These loci contain a cluster of cytokines and immune-related genes such as IL-13, IL-4, CD14, and IL-12B. Ying and colleagues<sup>101</sup> conducted a meta-analysis involving Asian (China, Japan, and Korea) and Caucasian (Spain, Germany and UK) subjects, and found that the functional single nucleotide polymorphism (SNP) rs20541 in the IL-13 gene was significantly associated with AR, particularly in Asians. However, inconsistent data from other studies suggest that rs20541 may explain little of the heritability of AR.<sup>130</sup> Recently, Li and colleagues<sup>131</sup> found that the DNA hypomethylation status of specific CpG islands located ~2 kb upstream of the IL-13 gene may be an independent risk factor for HDM-sensitive AR. Likewise, IL-4, another important Th2 cytokine gene, has multiple polymorphisms, including rs2243250, which regulates IL-4 gene expression and has been reported to be associated with AR in many ethnic groups (Chinese, Caucasian, and others).<sup>130</sup> The best gene-environment interaction presented in allergy to date should be SNPs in the CD14 gene, which plays a critical role in the innate immune response to microbial invasion. However, the association between CD14 genotypes and AR was found to be controversial in different studies in the Chinese population.<sup>114</sup> Except for HLA loci, chromosome 6 has several susceptible loci (TNFA, PBX, TAP1, IL17A, IL17F, and TNFAIP3) for AR. The study of Zhang and colleagues<sup>115</sup> demonstrated a genotype-dependant association pattern with regard to the SNP rs1799964 in the TNFA gene vs AR development in a Chinese population.

Some allergic airway inflammation and airway remodelling molecular genes have been shown to be as important as immune-related genes for AR susceptibility. Jin and colleagues,<sup>122</sup> have identified an association of a common functional SNP rs6265 in the brain-derived neurotrophic factor (BDNF) gene with AR risk and disease severity in 2 independent populations of Chinese patients with moderate-to-severe AR. A series of studies have focused on the correlation of the polymorphism based on the presence (insertion/deletion) of a non-sense DNA fragment in the angiotensin-converting enzyme (ACE) gene, exerting an anti-inflammatory effect by inactivating different proinflammatory peptides with and AR risk in different populations (also including Chinese populations).<sup>124-126</sup> Similarly, the association of T1, T2, V4, and Q-1 polymorphisms in Disintegrin with the metalloproteinase 33 (ADAM33) gene encoded for a protein important for airway remodelling and AR have also been investigated in some Chinese studies.<sup>127,128</sup>

To date, 3 genome-wide association studies (GWAS) have been performed specifically for the AR phenotype. Andiappan and colleagues<sup>132</sup> first employed GWAS strategy in a cohort of 4,461 ethnic Chinese individuals in Singapore and demonstrated that SNPs in mitochondrial ribosomal protein L4 (MRPL4) and B-cell adaptor for phosphatidylinositol 3-kinase (*BCAP*) were suggestively associated with AR. A recent study in a Han Chinese population demonstrated that SNPs in the *MRPL4* was strongly associated with the risk of AR.<sup>115</sup> However, other association signals have not yet replicated in other populations.

Despite the overlapping genetic susceptibility to AR in the Chinese population and other ethnic populations, genetic heterogeneity also plays an important role in explaining the apparent discrepancy in the genetic studies between races.

Although remarkable progress has been made in the genetics of AR and allergy, several limitations of these studies remain to be overcome; in particular, the confounding effects of endophenotyping, sample size, unmapping variants, epigenetic effects, gene-gene/gene-environment interactions, and functional validation. Furthermore, Zhang and colleagues<sup>103</sup> recently provided evidence that there are wide interactions among the crucial genes involved in the effector T-cell pathways and that the T helper 17 (Th17) pathway is a key player in developing susceptibility to AR. Therefore, future research should systematically integrate "overall data" from genomics, proteomics, epigenomics, and metabolomics to provide new insights into precision medical treatments for AR.

### 6.1.2 microRNA

Genetic regulation plays an undoubted role in the pathogenesis of AR. Because they function as endogenous inhibitors of translational processes, microRNA (miRNA/miR) is a class of short, noncoding RNAs that have emerged as important regulators of gene expression in the immune system.<sup>133</sup> Altered miRNA expression profiles have been identified in AR. In this regard, 7 up-regulated and 10 down-regulated miRNAs were recently identified in activated bone marrow-derived mast cells following IgE-FcεRI cross-linking with antigen, suggesting that these miRNAs may exert considerable influence on core signaling pathways and biologic behaviors.<sup>134</sup> Among these altered miRNAs, miR-21a-3p and miR-3113-5p were the most remarkably up-regulated and down-regulated miRNAs according to the bioinformatics algorithm.<sup>134</sup> Some miRNAs can modify the messenger RNA (mRNA) and protein expression of the chemokines and transcription factors directly. The miRNA microarray chip analysis has shown that miR-224, miR-187, and miR-143 were down-regulated in AR patients,<sup>135</sup> among which miR-143 has been shown to decrease the mRNA and protein expression levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), eotaxin, and mucin 5AC (MUC5AC) in IL-13-stimulated nasal epithelial cells through direct suppression of IL-13 receptor α1 chain (IL13Rα1).<sup>136</sup> This is particularly relevant as

IL-13 plays an important role in the pathogenesis of allergic inflammation. In addition, miR-135a can down-regulate the mRNA and protein expression levels of GATA-binding protein-3 and IL-4, and up-regulate the expression levels of T-bet and IFN- $\gamma$ , thus correcting the Th1/Th2 imbalance in AR mice.<sup>137</sup> The potential effects of miR-143 and miR-135a on signalling pathways in AR development are briefly illustrated in Fig. 5.

Some miRNAs could predict the onset of AR. Suojalehto and colleagues<sup>138</sup> have reported that miR-205, miR-155, and miR-498 were up-regulated in the nasal mucosa of currently symptomatic AR, whereas let-7e was down-regulated in currently nonsymptomatic AR. Notably, Chen and colleagues<sup>139</sup> found that miRNA-21 expression levels were significantly low in mononuclear leucocytes from cord blood samples with elevated cord blood IgE (CBiGE) and in monocytes from AR children, indicating that miRNA-21 may be an early predictor of AR and a possible therapeutic target for treating AR. However, further studies are needed reveal the full impact of miRNAs in the development of AR as well as to reveal their potential as therapeutic targets and noninvasive biomarkers in AR.

## 6.2 Immunopathogenesis

### 6.2.1 General concept

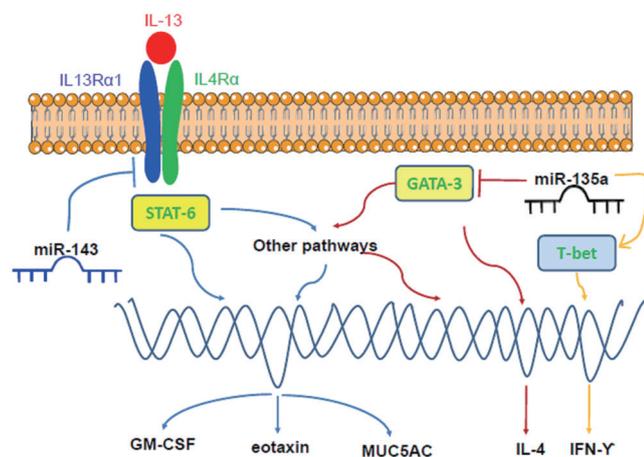
The symptoms of AR are a result of inhaled allergen-induced inflammation in the nasal mucosa, which is characterized by a Th2-dominated immune response associated with increased levels of serum IgE.<sup>140,141</sup>

Similar to other allergic diseases, the immune response in AR begins with sensitization. When the nasal mucosa is exposed to allergens, the allergens are captured and processed by antigen-presenting cells (mainly dendritic cells) and presented to naïve T cells. Naïve T cells then differentiate into Th2 cells which pro-

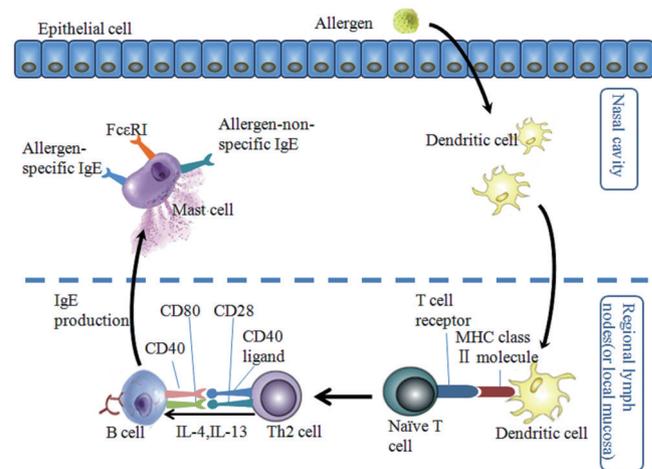
duce IL-4, IL-5, and IL-13. The IL-4 and IL-13 cytokines, together with the ligation of matched co-stimulatory molecules in Th2 cells and B cells, promote B cell phenotype switching to produce allergen specific IgE. Thereafter, the allergen-specific IgE binds to its high-affinity receptors (Fc $\epsilon$ R1) on the surface of mast cells and basophils, causing sensitization of these 2 cell types (Fig. 6).<sup>142</sup>

Re-exposure of sensitized individuals to the sensitizing allergens leads to a cascade of pathologic events, and subsequently the symptoms of AR. Allergic responsiveness can generally be divided into 2 phases: the immediate or early-phase and the late-phase responses.<sup>140</sup>

The early phase response occurs in sensitized individuals within minutes of allergen exposure, with mast cells and basophils being the best-known effector cells in this phase. Mast cells are abundant in the epithelial compartment of nasal mucosa in the sensitized individuals and can be easily activated upon re-exposure to the allergens. Cross-linking of the allergen-specific IgE-Fc $\epsilon$ R1 complexes on the mast cell and basophil surfaces by specific allergen triggers secretion of 3 classes of biologic products: those stored in cytoplasmic granules, lipid-derived mediators, and newly synthesized cytokines, chemokines, and growth factors as well as other products.<sup>140</sup> These mediators collectively result in vasodilation, increased vascular permeability, and mucus production, as well as stimulation of sensory nerves, which



**Fig. 5.** The potential effects of miR-143 and miR-135a on signaling pathways. While miR-143 can inhibit the expression of GM-CSF, eotaxin, and MUC5AC by suppressing the IL13Ra1 signalling pathway, miR-135a can down-regulate the mRNA and protein expression levels of GATA-3 and IL-4 and up-regulate the expression levels of T-bet and IFN- $\gamma$ , thereby correcting the Th1/Th2 imbalance.



**Fig. 6.** The process of allergen sensitization in AR. Following exposure of nasal mucosa to allergens, allergens are captured, taken up, and processed by dendritic cells (DCs). Subsequently, DCs are activate and mature, and migrate to regional lymph nodes or to sites in the local mucosa, where they present allergen-derived peptides in the context of MHC class II molecules to naïve T cells. Naïve T cells then differentiate into Th2 cells, which produce IL-4 and IL-13 in the presence of early IL-4. In the presence of these Th2-derived cytokines, together with ligation of the suitable co-stimulatory molecules (CD40 ligand with CD40 and CD28 with CD80), B cells undergo immunoglobulin class-switch recombination to produce IgE antibodies. The locally and/or systemically diffused IgE binds to the high-affinity receptors (Fc $\epsilon$ R1) on mast cells and basophils (not shown), and results in sensitization of these cells (adapted from Galli and colleagues [142]).

evoke the symptoms of nasal itching, rhinorrhea, sneezing and congestion (Fig. 7).<sup>142</sup>

Late-phase reaction typically develops at 2 to 6 hours after allergen exposure and is characterized by a prolongation of sneezing, rhinorrhea and a predominantly sustained nasal congestion. A variety of mediators and cells are involved in this phase. Some mast-cell products such as TNF- $\alpha$ , LTB<sub>4</sub>, IL-5, and IL-8/CXCL8 have the potential to recruit and activate other immune cells including monocytes, T cells, eosinophils and basophils. The released products of mast cells (e.g. histamine, LTB<sub>4</sub>, PGD<sub>2</sub>, and TNF- $\alpha$ ) can also modulate the activity of dendritic cells, T cells and B cells, or influence structural cells (including vascular endothelial cells, epithelial cells and nerve cells). On the other hand, some mast cell products (e.g. IL-10 and TGF- $\beta$ ) have anti-inflammatory or immunosuppressive functions. The recruited immune cells, however, may lead to some tissue damage and remodelling, for example, eosinophil basic protein induces epithelial cells injury, and Th2 cytokines (IL-4, IL-5, and IL-9) provoke more IgE production, goblet cell hyperplasia, and excess mucus production (Fig. 7).<sup>142</sup>

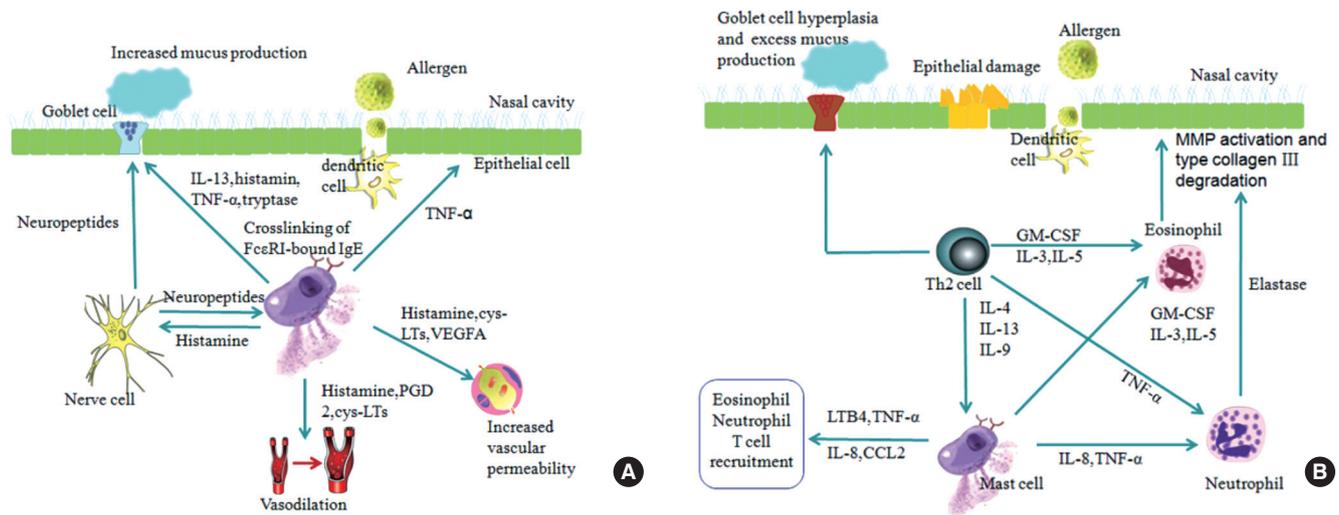
In addition to the common pathophysiological pathways detailed above, other mechanisms are also likely to be involved in AR. Although epithelial cells are important structural cells playing major roles in providing an effective barrier to entry of foreign particles, secretion of mucus, and removal of foreign agents by virtue of possessing cilia, increasing evidence shows that ep-

ithelial cells also have potent immunomodulatory activities through synthesizing and releasing cytokines and chemokines (e.g. CCL2, CCL20, GM-CSF, IL-1 $\beta$ , TSLP, IL-25, and IL-33).<sup>143</sup> The epithelial cytokines and chemokines mediate the cross-talk between epithelial cells and immune cells,<sup>144</sup> and thus bridge the innate and adaptive immunity in nasal tissues. Nasal epithelial cells in patients with AR may also play a role in antigen presentation through enhanced expression of HLA-DR and CD86.<sup>145</sup> It has been proposed that diesel exhaust particles disrupt tight junctions and increase the paracellular permeability in RPMI 2,650 cells (a human nasal epithelial cell line) *in vitro*.<sup>146</sup>

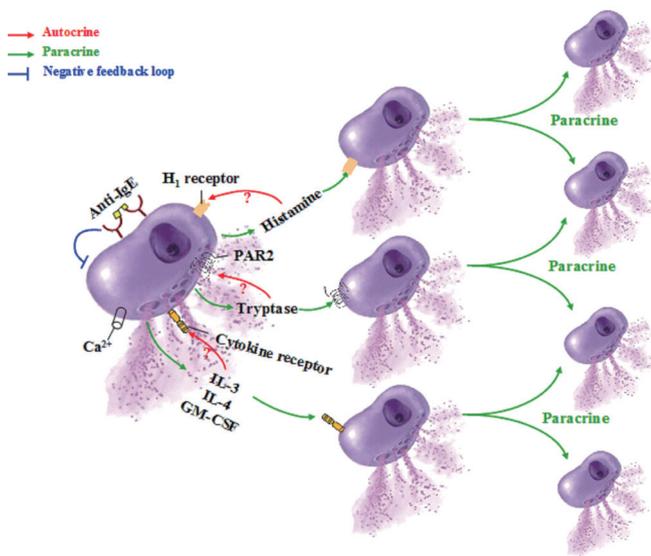
Evidence from some recent studies suggests that regulatory T cells (Treg)<sup>147</sup> and Th17 cells,<sup>148</sup> type 2 innate lymphoid cells,<sup>149</sup> miRNA,<sup>137,150</sup> follicular Th cells,<sup>151</sup> and regulatory B cells<sup>151</sup> may also play a role in AR. Indeed, apart from the well-documented classic immunopathologic mechanisms of AR, the following potential immunologic mechanisms may play key roles in AR.

### 1) Self-amplification mechanisms of mast cell activation

It has previously been advocated that at least 2 pathways exist in humans for mast cells to amplify their own activation-degranulation signals in an autocrine or paracrine manner,<sup>152</sup> which may partially explain the phenomena that when a sensitized individual contacts allergen only once, the local allergic response in the involved tissue or organ may last for days or weeks. These pathways include the tryptase-protease-activated receptor (PAR)-



**Fig. 7.** Early and late phase reactions in AR. (A) Early phase reaction: Ligation of allergen-specific IgE-Fc $\epsilon$ R1 complexes by the corresponding allergen on mast cells activates mast cells to secrete preformed mediators (e.g. histamine and tryptase) and lipid-derived mediators (e.g. PGD<sub>2</sub>, LTB<sub>4</sub> and PAF), which increase vascular permeability, mucus secretion, and blood vessel dilation. This results in watery rhinorrhea, mucosal edema, and nasal congestion. Stimulation of sensory nerves in the nose results in sneezing and sensations of nasal itch and congestion (adapted from Galli and colleagues [142]). (B) Late phase reaction: Ligation of IgE-Fc $\epsilon$ R1 complexes by allergen on mast cells results in release of newly synthesized cytokines, chemokines and growth factors, which contribute to the late phase reaction. Mast cells promote the influx and activation of inflammatory leukocytes (such as neutrophils, eosinophils and T cells) by producing TNF- $\alpha$ , LTB<sub>4</sub>, IL-5, IL-8, and CCL2. T cells that recognize allergen-derived peptides also release products (e.g. IL-4, IL-13, and IL-9) and contribute to late-phase reactions. IL-4 and IL-13 released by Th2 cells can stimulate mast cells to produce more IgE and induce goblet cell hyperplasia, which results in excess mucus production. The recruited immune cells have some downstream effects. For example, elastase released by neutrophils promotes activation of matrix metalloproteinases and degradation of type III collagen. Basic proteins released by eosinophils can cause epithelial cell damage (adapted from Galli and colleagues [142]).



**Fig. 8.** Self-amplification mechanisms of mast cell degranulation. IL, interleukin; GM-CSF, granulocyte/macrophage colony-stimulating factor; PAR, protease activated receptor (adapted from He and colleagues [152]).

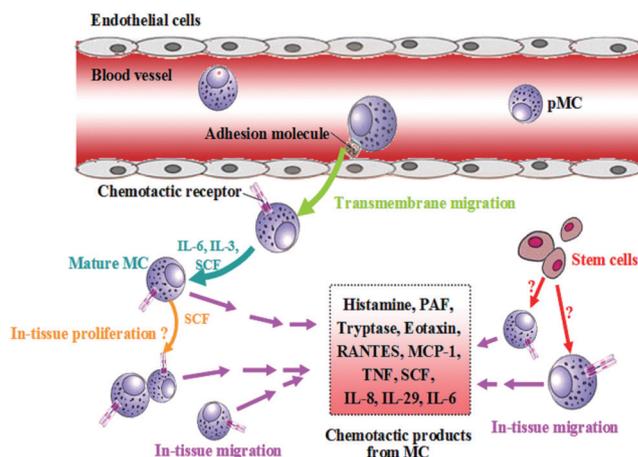
2 pathway and the histamine- $H_1$  receptor pathway (Fig. 8).

Several self-amplification mechanisms of mast cell activation have been reported. For example, while IL-36 released from the mast cells<sup>153</sup> can selectively induce retinaldehyde dehydrogenase-II release<sup>154</sup> from mast cells, GM-CSF secreted from mast cells<sup>153,155</sup> is able to induce IL-4 release from mast cells.<sup>156</sup> IL-4 secreted from mast cells<sup>157</sup> can in turn amplify the classic Fc epsilonRI-dependent mast cell activation and release of cysteinyl leukotrienes,<sup>158</sup> and in synergy with stem cell factor (SCF), IL-4 strongly enhances mast cell proliferation and shifts IgE-dependent cytokine production in mature human mast cells toward an increased release of Th2 cytokines IL-5, and IL-13.<sup>159</sup>

### 2) Self-amplification mechanisms of mast cell accumulation

The fundamental requirement for paracrine self-amplification mechanisms of mast cell activation is the presence of a relatively high density of mast cells in the involved tissues. It has long been recognized that the numbers of mast cells in allergic tissues such as lung<sup>160</sup> and skin<sup>161</sup> are dramatically increased, but the mechanisms through which mast cells are accumulated remain obscure. Generally speaking, mast cells can be accumulated by 2 mechanisms: (1) migration from adjacent tissues or from blood and (2) local generation in the tissue (Fig. 9).

Numerous mast cell products have been found to be able to induce mast cell migration. Thus, while histamine has been shown to induce chemotaxis of mouse mast cells through histamine  $H_1$  receptor,<sup>162</sup> PAF has been identified as a potent chemoattractant of both murine and human mast cells.<sup>163</sup> Interactions of eotaxin, RANTES, and MCP-1 with CCR3 on basophils and mast cells are responsible for the recruitment of these cells.<sup>164</sup> While IL-6<sup>165</sup> and TNF<sup>166</sup> stimulate migration of mast cells in the



**Fig. 9.** Self-amplification mechanisms of mast cell accumulation. IL, interleukin; pMC, progenitor mast cell; MC, mast cell; SCF, stem cell factor; TNF, tumor necrosis factor; RANTES, regulated upon activation normal T cell expressed and secreted; MCP-1, monocyte chemoattractant protein-1; PAF, platelet-activating factor (adapted from He and colleagues [152]).

presence of laminin, IL-4 induces homotypic aggregation of human cord blood mononuclear progenitor cells (hCBMCs) in the presence of SCF and IL-6.<sup>167</sup> SCF by itself is capable of inducing the migration of mast cells via its receptor c-Kit.<sup>168</sup> Moreover, IL-29 has been found to be released from mast cells and is able to induce mast cell infiltration in mouse peritoneum by a CD18- and ICAM-1-dependent mechanism.<sup>169</sup> Mast cells are found to express and release significantly higher concentration of IL-8 and expression of IL-8 receptors CXCR1 and CXCR2, through which IL-8 recruits mast cells.<sup>170</sup>

Little is known about whether mast cells can be generated in tissue, but a report that two-thirds of freshly dispersed mast cells from skin cultured with recombinant human SCF showed evidence of proliferation suggests that mast cells may have the ability to proliferate in skin tissue.<sup>171</sup> Although there is a lack of direct evidence that mast cells can be derived from tissue stem cells, the finding that mast cells can be obtained from bone marrow and cord blood CD34<sup>172</sup>- or CD133<sup>173</sup>- positive progenitor cells<sup>173</sup> in the presence of IL-6 and SCF,<sup>174</sup> strongly suggests that tissue stem cells could possibly be driven to differentiate into mast cells under inflammatory conditions.

### 3) Influence of mast cell mediators on secondary effector cells of allergy

While activation of primary effector cells, including mast cells and basophils, is a key element of allergic disease, stimulation of secondary effector cells of allergy such as eosinophils and neutrophils also plays also a crucial role in particularly the late-phase reactions. A review of studies investigating the role of human mast cell-derived cytokines has substantially described the pivotal interaction between mast cells and eosinophils in eosinophil-mediated inflammatory responses.<sup>175</sup> In addition,

**Table 5.** Characteristics of subsets of Treg cell

Subset	Specific markers	Secretory products	Actions	Location
nTreg	CD4, CD25, Foxp3	IL-10, TGF- $\beta$	Block T cell proliferation, suppression of DCs, inhibition of effector Th1, Th2 and Th17 cells; eliminate production of allergen-specific IgE, induce IgG4 secretion; suppress mast cells, basophils and eosinophils; interact with resident tissue cells and participate tissue remodelling	Thymus [188]
ICOS(+) Treg	CD4, CD25, Foxp3, ICOS	IL-10, IL-17, IFN- $\gamma$	Suppress hapten-reactive CD8(+) T cells	Generated from nTregs
iTreg	CD4, Foxp3	IL-10, TGF- $\beta$	Similar to nTreg	Periphery
Tr1	CD4, CD25	IL-10	Suppress effector Th cell migration and functions [186]; suppress mast cells, basophils, and eosinophils [187]	Generated from non-Treg cell precursors and home lungs, and draining lymph nodes
CD8(+)Treg	CD8, Foxp3, CD25 (not for tonsil origin), CD28	IL-10, TNF- $\alpha$ , IFN- $\gamma$ , GB	Block activation of naïve or effector T cells; suppress IgG/IgE antibody responses [188], IL-4 expression, and the proliferation of CD4(+) T cells.	Generated from OT-1 CD8 cells [188] and tonsils
IL-17-producing Foxp3 (+) Treg	CD4, Foxp3, CCR6, ROR-GT	IL-17	Inhibit the proliferation of CD4(+) effector T cells [189].	Differentiated from CD4(+)Foxp3(+) CCR6(-) Tregs in peripheral blood and lymphoid tissue [189]

nTreg, natural regulatory T cell; ICOS, inducible costimulator; iTreg, inducible/adaptive regulatory T cell; Tr1 cell, IL-10-producing type 1 regulatory T cell; GB, granzyme B; RORGT, ROR gamma transcription factor (adapted from Zhang and colleagues [183]).

TSLP, IL-25,<sup>176</sup> and IL-31<sup>177</sup> have recently been shown to be able to activate eosinophils and to contribute to allergic inflammation. Mast cell products, including tryptase,<sup>178</sup> chymase,<sup>179</sup> MMP-9,<sup>180</sup> heparin,<sup>181</sup> IL-8 and TNF,<sup>182</sup> are also potent chemoattractants for neutrophils and may be responsible for the cross-talk between mast cells and neutrophils. As large numbers of eosinophils and neutrophils can reside in the involved tissue and are able to release an array of proinflammatory mediators, these cells also play an important role in the etiology of allergic disease. However, the mechanisms underlying allergens to selectively accumulate and activate eosinophils and neutrophils via mast cells remain obscure.

#### 4) Contribution of Tregs to AR

In recent years, Tregs have emerged as key cells involved during the sensitization phase of the pathogenesis of allergy.<sup>183</sup> It is recognized that acquired immunity is controlled by Tregs that suppress responses of effector T cells. Tregs can be classified into natural Tregs (nTreg)<sup>184</sup> including inducible costimulator (ICOS)(+) Tregs,<sup>185</sup> inducible/adaptive Tregs (iTreg),<sup>186</sup> IL-10-producing type 1 Tregs (Tr1 cells),<sup>187</sup> CD8(+) Tregs<sup>188</sup> and IL-17-producing Tregs.<sup>189</sup> These cells share some common features including expression of Foxp3 (except for Tr1 cells) and secretion of inhibitory cytokine IL-10 and/or TGF- $\beta$  (Table 5). It is apparent that Tregs are likely contribute to allergic disorders and play a crucial role in the treatment of allergy through their actions on suppression of effector T cells and inhibition of activation of mast cells and basophils. Thus, modulation of the functions of Tregs may provide a novel strategy for preventing and treating allergic diseases.

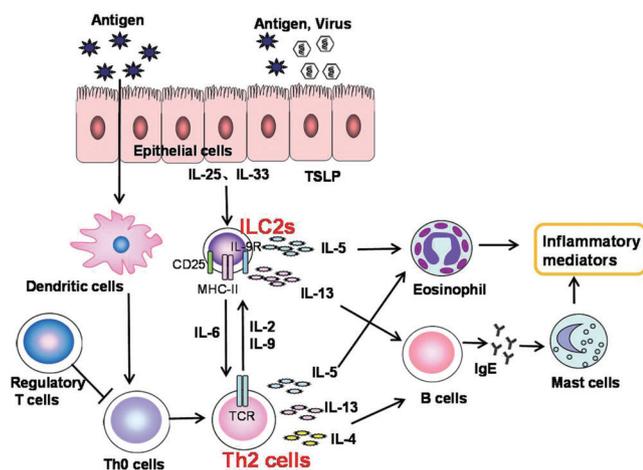
There is increasing interest in the role of both nTreg and iTreg

populations in preventing hypersensitive immune responses and the underlying sensitization to allergens. It was speculated as early as 2006 that Tregs may actively prevent Th2 responses to allergens occurring in healthy nonatopic individuals and that their functions may be impaired in allergic patients.<sup>190</sup> It has been suggested that peripheral T-cell tolerance to environmental antigens is crucial for the avoidance of allergy and that aberrant activation of Th2 cells in allergy is secondary to impaired mechanisms of peripheral T-cell tolerance normally mediated by antigen-specific T-cell anergy, Tregs and the suppressive cytokines IL-10 and TGF- $\beta$ . Therefore, the most appealing therapy for allergic diseases would be allergen-specific immunotherapy<sup>191</sup> that reduces Th2 cytokine production and promotes induction of anergy, Treg, and suppressor cytokines.<sup>192</sup>

A study which investigated allergen-induced Th2, Th1 and Treg immune responses in peripheral blood mononuclear cells (PBMC), and their association with symptom improvement in AD patients after 3 years of AIT showed that both IL-4 expression and the IL-4/IFN-gamma ratio were decreased in patients with a good therapeutic outcome after 1 year of AIT, whereas the induced Treg and Th1 responses persisted over 3 years after AIT.<sup>193</sup>

#### 6.2.2 Innate type 2 immune response

CD4+ Th2 cells play a significant role in AR. Indeed, type 2 cytokines produced by Th2 cells such as IL-4, IL-5 and IL-13 drive many features of allergic rhinitis. Group 2 innate lymphoid cells (ILC2s) are a newly recognized subset of the innate lymphoid cell family, which rapidly and dramatically produces IL-5 and IL-13 in response to IL-25 or IL-33<sup>194-196</sup> and is likely to play a role in the etiology of AR (Fig. 10). ILC2s are morphologically similar to, but smaller than lymphocytes. ILC2s lack T-cell, B-



**Fig. 10.** The role of ILC2 in AR. Type 2 responses are initiated by allergens that disrupt the epithelial barriers and induce secretion of IL-25, IL-33, and TSLP. IL-25 and IL-33 activate ILC2s to produce the type 2 cytokines IL-5 and IL-13. Epithelial cytokines also activate DCs to induce Th2 responses. Secretion of IL-5 by ILC2s leads to the recruitment and activation of mast cells and eosinophils. The activation of T cells further amplifies the secretion of type 2 cytokines, and the production of IL-4 and IL-13 by T cells leads to the production of IgE by B cells. Together, the responses triggered by secretion of type 2 cytokines from ILC2s and Th2 cells play an important role in inducing allergic inflammation.

cell, natural-killer cell or other cell lineage markers, but express the IL-7 receptor  $\alpha$ -chain (CD127), c-Kit, Sca-1, *etc.*<sup>194,195,197-199</sup> ILC2s produce dramatic amounts of IL-5 and IL-13, and some IL-4 in response to the Th2 cell-stimulating cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) produced by epithelial cells.<sup>200-204</sup> The discovery of ILC2s puts forward a new challenge to the traditional opinions that T helper type 2 (Th2) cells play a dominant role in Th2-skewed allergic diseases. There may, however, be some interactions between ILC2 and Th2 cells via some cytokines as shown in Fig. 10. ILC2s may interact with T cells through both cytokine secretion and specific molecules on the cell surface. ILC2s may regulate T cell differentiation through antigen presentation via major histocompatibility complex (MHC) class II and through the production of IL-6. In turn, T cells support the maintenance and proliferation of ILCs through production of IL-2 and IL-9.<sup>205</sup>

ILC2s have been reported to be involved in the pathology of both asthma and AR in animals and humans. Studies of adaptive immunodeficiency mice have demonstrated that influenza-,<sup>206</sup> protease-,<sup>207</sup> ryegrass-<sup>208</sup> or mite-induced<sup>209</sup> airway hyper-reactivity or asthmatic inflammation is mediated via ILC2s. In addition, ILC2s have also been found to be increased in several allergic immune diseases in humans, such as AD,<sup>210,211</sup> active eosinophilic esophagitis<sup>212</sup> and CRS with nasal polyps or eosinophilia.<sup>213,214</sup> Moreover, high ILC2 levels have been found in patients with even moderate-to-severe asthma,<sup>215</sup> persistent airway eosinophilia<sup>215</sup> or rhinovirus-induced asthma exacerbations.<sup>216</sup> Importantly, increased peripheral ILC2s have been re-

ported in AR patients during the grass pollen season<sup>217</sup> or after the challenge with cat antigen.<sup>149</sup>

More recent evidence from a study in Chinese subjects has indicated that the percentage of ILC2s was significantly elevated in HDM-sensitized AR patients, compared to mugwort-sensitized AR patients and healthy controls, with no significant difference between the latter 2 groups.<sup>218</sup> Importantly, peripheral ILC2 levels in HDM-sensitized AR patients were strongly correlated positively with the severity of the clinical VAS score and with the plasma levels of their functional cytokine IL-13.<sup>219</sup> Moreover, stimulation with IL-25 and IL-33 induced significantly greater production of IL-5 and IL-13 in peripheral blood mononuclear cells (PBMCs) of HDM-sensitized AR patients than in those of mugwort-sensitized AR patients or healthy controls.<sup>218</sup> The levels of IL-5 and IL-13 were also higher following stimulation with IL-25 and IL-33 compared to stimulation with DerP1 stimulation.<sup>219</sup> Similarly, sorted ILC2s from AR patients produced large amounts of IL-5 and IL-13 after stimulation with IL-25 and IL-33. Furthermore, a prospective study has investigated the effects of glucocorticoid treatment on the levels and function of ILC2s in patients with asthma or asthma plus AR.<sup>220</sup> The study showed high frequency of ILC2s in human PBMCs from both groups of patients with asthma or asthma plus AR, and demonstrated that ILC2 levels significantly decreased to normal levels 3 months after glucocorticoid treatment. Collectively, these findings suggest that sensitizing allergen type may be an important factor determining the functional profile and frequency of ILC2s in AR patients and that high levels of innate type 2 immune responses in AR may provide a potential strategy for mediating the immunopathogenesis and therapy of this disease.

### 6.3 Inflammatory mediators

#### 6.3.1 Chemokines and receptors

Chemokines are a group of cytokines responsible for the activation of leukocytes, such as T/B lymphocytes, monocytes, neutrophils, eosinophils and basophils, which are associated with allergic inflammation. It is now generally accepted that several chemokines and their receptors play essential roles in the pathogenesis of AR.

Eotaxin is thought to be associated with allergic inflammation as it is involved in the recruitment and activation of eosinophils by chemotaxis after antigen challenge in AR patients.<sup>221</sup> Eotaxin exists in 3 isoforms: eotaxin-1 (CCL11), eotaxin-2 (CCL24) and eotaxin-3 (CCL26). Eotaxin can accelerate basophilic cell degranulation, accumulate eosinophils, and then further induce an allergic reaction through the IgE-mast-cell-Fc $\epsilon$ RI cascade.<sup>222</sup> Regulated upon activation normal T cell expressed and secreted factor (RANTES/CCL5) is another chemokine closely associated with allergic inflammation and is found to be highly expressed in the epithelial and endothelial cells of the lower nasal mucosa in AR.<sup>223</sup> RANTES contributes to eosinophil-mediated

inflammatory responses in the earlier period of allergic reaction.<sup>224</sup>

Cytokines and chemokines produce marked effects via the receptors of chemokines. Among them, the most important eosinophil chemokine receptor is CCR3, which ligands with eotaxin-1, eotaxin-2, eotaxin-3, and RANTES to activate eosinophils to release granules.<sup>225,226</sup> Other receptors such as CCR4 and CCR8 expressed on eosinophils, mast cells and basophils are also associated with AR.<sup>227</sup> Thus, this subset of chemokines and chemokine receptors are potentially important in modulating immune responses by amplifying Th2 cell responses in AR.

### 6.3.2 Nasal nitric oxide (NO) and gasotransmitters

The oxidant/antioxidant imbalance is also an important part of the pathogenesis of AR as allergens can stimulate the generation of reactive oxygen species, which can cause nasal mucosal epithelial damage. This induces inflammatory cells to release inflammatory mediators such as cytokines, chemokines and adhesion molecules, and lead to the development of further inflammation and damage. Additionally, some small gaseous molecules known as gasotransmitters have also been shown to play important roles in regulating the oxidation process in AR.<sup>228</sup>

The first gasotransmitter identified was nitric oxide (NO).<sup>229</sup> An increasing body of evidence has indicated NO production to be increased in both perennial and seasonal AR,<sup>194</sup> with many studies indicating nasally exhaled NO in humans to be generated mainly within the mucosal epithelium of the paranasal sinuses.<sup>230</sup> Furthermore, increased local concentrations of NO in AR tend to increase Th2 cell-synthesized interleukins, including IL-4, IL-5, and IL-10, which promote the production of IgE and accumulation of eosinophils. NO also tends to increase edema and plasma exudation, and cause denudation and desquamation of the epithelial lining.<sup>231</sup>

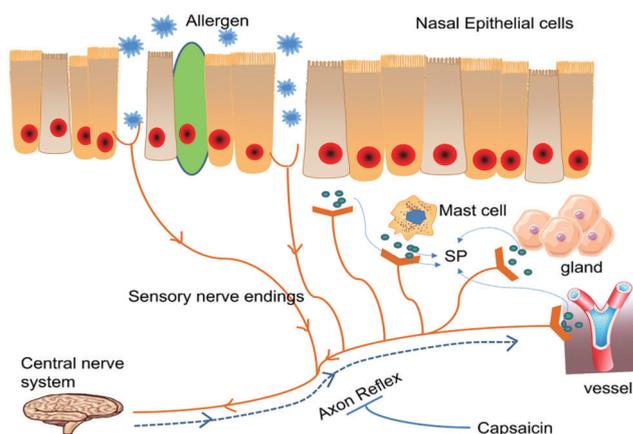
Carbon monoxide (CO) and hydrogen sulfide (H<sub>2</sub>S) have also been identified as gasotransmitters, which participate in the resolution of allergy-induced airway inflammation.<sup>232</sup> While exhaled CO has been implicated as a likely gasotransmitter in the development of asthma, its role in the development of AR is less clear, despite being generated in the nasal mucosa of AR.<sup>233</sup> Similarly, the role of H<sub>2</sub>S in the pathogenesis of AR is also unclear. A previous study in humans has suggested that this gasotransmitter may have multiple functions in human nasal mucosa and contribute to the development of allergic symptoms such as rhinorrhea, sneezing and nasal stuffiness.<sup>234</sup> However, other studies on the regulation of the endogenous H<sub>2</sub>S pathway in the nasal mucosa of an AR guinea pig model has suggested that H<sub>2</sub>S may exert anti-inflammatory as well as antioxidant effects in the nasal mucosa and therefore may serve a protective function in AR patients.<sup>235</sup>

### 6.3.3 Substance P

Substance P (SP) is a neuropeptide neurotransmitter that be-

longs to the tachykinin family of peptides, which can be released by C-nerve fibers in the nasal mucosa. It has been found to have a variety of proinflammatory and prosecretory effects in epithelial, glandular and vascular tissues in the nasal cavity and thus play an important role in neurogenic inflammation.<sup>236</sup> The nasal mucosa is densely innervated by sensory nerve fibers that release SP, which leads to vascular permeability, plasma extravasation, glandular secretion and proinflammatory cell influx.<sup>237</sup> Stimulation of the nasal mucosa by SP induces the release of histamine and thereby influences the physiologic and pathophysiological nasal conditions, especially during allergic inflammatory processes. Using capsaicin as a blocking agent of SP experiments on AR animal models, Zhang and colleagues<sup>238</sup> have shown that capsaicin could effectively deplete the concentration of SP in the nasal mucosa and thus relieve the various symptoms of AR in these animals. Intranasal administration of capsaicin in the treatment of patients with AR has also demonstrated to relieve clinical symptoms of AR and to markedly reduce the concentration of SP in the nasal secretions.<sup>239</sup> These studies indicated that the therapeutic mechanism of capsaicin in AR was related to the blocking of axon reflex, via which stimulation of allergen on sensory nerve fibers may lead to the release of SP (Fig. 11).

There is some evidence that the expression of endogenous SP mRNA and peptide is significantly increased under IgE-activated conditions and that small hairpin RNA (shRNA)-mediated knockdown of endogenous SP can reduce the ability of IgE-activated mast cells to undergo degranulation.<sup>240</sup> This finding suggests that endogenous SP plays an important role in mast cell antigen-mediated degranulation and thus enhances the progression of allergic inflammation.<sup>240</sup> Indeed, it is notable that SP is expressed not only by neurons, but also in immune cells such as mast cells<sup>240</sup> which release allergic mediators such as histamine,<sup>241</sup> thereby exacerbating allergic symptoms. It is possible that widespread expression of SP in diverse cell types may indi-



**Fig. 11.** Stimulation of allergen on C fibers may lead to the release of substance P via axon reflex.

cate a multifunctional role for SP in a wide variety of physiologic and pathophysiologic conditions by activating a multitude of signalling pathways. Moreover, SP acts via neurokinin-1 receptors (NK-1R) to stimulate the release of inflammatory mediators including histamine and chemokines, which recruit inflammatory cells. Knockdown of NK-1R expression effectively inhibits NK-1R expression, and alleviates AR-related clinical symptoms and eosinophil inflammation in the nasal mucosal tissues of rats, suggesting that NK-1R may play an important role in the development of AR.<sup>242</sup>

## 6.4 Environmental factors

### 6.4.1 Pollen

Pollens are important inhalant allergens as a cause of allergic disease. Pollen grains deposit on the nasal mucosa and release allergenic proteins to cause specific IgE and responses to pollen allergen, which are characterized by increased expression of Th2 cytokines. Allergic disease caused by pollen allergens is known as “pollinosis”. According to a study by Zhang and colleagues,<sup>20</sup> the prevalence of pollen-related AR in China is 47.8%. The main airborne allergic pollens come from wind-pollinated plants rather than insect-pollinated plants and have their own characteristics to facilitate wind dispersion. These pollens are small (diameter 10–100  $\mu\text{m}$ ), light, and prolific with some conifer pollen developing air sacs to make it easy to become airborne. The allergic pollens also demonstrate seasonality and regionalism. The florescence of allergic plants is influenced by meteorological factors.

Tree and weed pollens are the main pollen allergens in China.<sup>243</sup> Qiao and colleagues<sup>244</sup> first collected the common airborne pollens and -plants in China and documented these as a compilation of “*Airborne pollens and plants in China.*” Most tree plants flower from March to May, and weed plants from July to October. The differences in the geography and climate result in the diversification of florescence in different regions of China. *Artemisia*, *Humulus*, and *Amaranthaceae* are the major weeds that cause late summer and fall seasonal pollinosis. The principal tree pollens in North China come from the cold-resistant trees such as *Populus* and *Salix*, whereas in South China the tree pollens are mainly from *Broussonetia*, *Melia*, and *Casuarina-trees*.<sup>243</sup>

A study conducted between November 2003 to October 2004 to investigate the general and seasonal distribution of airborne pollens and their relationship with pollinosis in 16 areas in 12 cities in Hubei province, Central China, identified 61 pollen genera within the 257, 520 pollen samples collected.<sup>245</sup> The peak airborne pollen distribution occurred in 2 seasons each year, spring (March and April) and autumn (August to October), and pollinosis corresponded to the peak pollen distribution. Similarly, another study of airborne pollens performed in Beijing indicated that the summer-autumn pollen concentration peaked from August 20 to September 15, with the major pollens being

*Artemisia L*, *Chenopodium album*, and *Humulus scandens*.<sup>246</sup> There was a significant correlation between specific pollen concentration and the number of patients sensitized to a particular pollen as well as between pollen exposure and the onset of symptoms of AR.<sup>246</sup>

### 6.4.2 Traditional pollutants

In urban and suburban areas, industrial facilities and transportation-related emissions are major sources of air pollution. The main air pollutants include carbon oxides ( $\text{CO}_x$ ), nitrogen oxides ( $\text{NO}_x$ ), ozone ( $\text{O}_3$ ), sulphur dioxide ( $\text{SO}_2$ ), and PM—a complex mixture of chemicals and particles of which diesel exhaust particles (DEPs) are the largest single component.<sup>247</sup>

Increasing evidence shows that air pollution is associated with respiratory diseases, particularly AR. A study assessed the potential effects of PM10,  $\text{SO}_2$ , and  $\text{NO}_2$  on outpatient visits caused by AR in Beijing during the period 2009–2010 and found strong associations between the daily concentrations of the 3 air pollutants and the daily number of outpatients for AR.<sup>248</sup> Similarly, another study of 32,143 Taiwanese school children indicated that persistent exposure to  $\text{NO}_x$ , CO, and  $\text{SO}_2$  may increase the prevalence of AR.<sup>249</sup>

Several molecular mechanisms underlying the effects of air pollution on allergic respiratory disease have been explored in animal and human studies. First, air pollution may enhance IgE production by stimulating B lymphocytes. Diaz-Sanchez and colleagues<sup>250</sup> showed that exposure to DEPs significantly increased IgE levels in human nasal fluids by greatly increasing the number of IgE-secreting cells and by altering the expression of IgE mRNA isoforms. This suggests that DEP exposure *in vivo* induces both a quantitative increase in IgE production and a shift in the type of IgE produced. Secondly, air pollution may increase the levels of some proinflammatory cytokines. The study of Diaz-Sanchez and colleagues<sup>250</sup> also showed that nasal challenge in healthy humans with 0.15 mg DEPs suspended in 200  $\mu\text{L}$  of saline expressed the TH2-type cytokines IL-4, IL-5, IL-6, and IL-10 in their nasal mucosal cells 18–24 hours after exposure. Indeed, studies have demonstrated that DEPs may enhance the symptoms of allergic rhinitis by synergistic action with pollen resulting in increased production and secretion of inflammatory cytokines such as IL-4, IL-5, and IL-13<sup>251</sup> as well as enhanced local IgE production accompanied by isotype switching from IgM or IgD to IgE antibody in nasal lavage cells.<sup>252</sup> Moreover, nasal histamine levels after challenge with dust mite allergen in dust mite-sensitive subjects were increased 3-fold when DEPs were coadministered with the allergen.<sup>253</sup> Thirdly, air pollution may enhance reactive oxygen species (ROS) production. ROS such as superoxide, hydrogen peroxide and hydroxyl radical react with proteins, lipids, and DNA, and then lead to cellular damage. Finally, air pollution may enhance the immune response to allergens by physically binding with them. For example, one study has demonstrated that incubation of DEPs with

purified natural grass pollen allergen Lol p1 for 30 minutes resulted in the binding of Lol p1 to DEPs with sufficient strength, which could not be removed by different washing methods.<sup>254</sup> However, by employing this mechanism, DEPs may be transported with allergens, such as pollen grain fragments, into human airways, where both agents may be deposited on the mucosa at the same location and the close proximity of the DEPs and allergens would facilitate synergistic immunologic responses and respiratory symptoms.<sup>255</sup>

### 6.5 Nutrition and intestinal flora

In recent years, nutrition has been thought to play a role in the pathogenesis of AR,<sup>256-258</sup> with several studies from China and other countries demonstrating a relationship between AR and nutrition.<sup>123,256,259,260</sup>

The mechanisms underlying the effects of nutrition in the pathogenesis of AR are poorly understood, but epigenetic modulation<sup>261</sup> and immunobiologic processes<sup>258,262</sup> may be involved. Epigenetic modulation (including DNA methylation, histone modifications and miRNA) refers to chemical reactions that switch parts of the genome on and off, thereby changing gene expression,<sup>261</sup> which may influence AR-related immune responses. Evidence of nutrition-induced epigenetic changes in patients with allergy and atopy has been found for nutrients, including folic acid and fish oil, and in obesity itself.<sup>261</sup> As for immunobiologic processes, immunoregulatory effects and airway epithelial cell responses appeared to be involved when AR patients or AR animal models were exposed to some nutrients such as ginger,<sup>258</sup> vitamin D and vitamin E.<sup>262</sup>

On the other hand, epidemiologic studies have noted associations between deficiency in microbial exposure in early life and increasing risk of allergies in childhood. After neonates are born, microbes begin to colonize in their oral, respiratory and gut tracts. The microbial communities, in turn, are influenced by an array of environmental factors, early life local microbial exposures, delivery mode,<sup>263</sup> diet,<sup>259</sup> antimicrobial administration, physiologic factors, mental stress, *etc*, which are characterized by fluctuating microbial diversity. The neonatal gut microbiome plays an instrumental role in the development and function of childhood immune system,<sup>264</sup> with the interaction between intestinal flora in early life and the mucosal immune system influencing the induction of immune tolerance or immune imbalance.

Microbial colonization patterns in very early life may influence immune development and function in key-time mode.<sup>265</sup> Neonatal immune cells are different from mature cells and can learn to tolerate the symbiotic bacteria in an age-dependent manner. Once the critical 'window of opportunity' of immunologic development is missed, intestinal immune development cannot be fully achieved in the adult and subsequently allergic disease develops.

### 6.6 Pathogenesis and syndrome differentiation in TCM

#### 6.6.1 Theories related to TCM

The origin of TCM can be traced back to remote antiquity. In its long course of development, TCM has gradually evolved into a unique and integrated system of medicine and an important part of Chinese culture. Huangdi Neijing (Huangdi's Canon of Medicine), the "Bible" for TCM published over 2000 years ago, is the earliest and greatest medical classic extant in China. The content of Huangdi Neijing covers the theories of yin-yang and Zangxiang. The theory of yin-yang permeates through all aspects of the theoretical system of TCM. Physiologically, the theory of yin-yang holds that the normal life activities of the human body result from the coordination between yin and yang in a unity of opposites, and pathologically TCM considers that the imbalance between yin and yang is one of the basic causes for the pathogenesis of disease. Based on this determination, right herbs are selected according to their yin or yang properties to rectify the imbalance of yin and yang, eventually achieving the purpose of curing the disease.

The theory of Zangxiang studies the physiologic and pathologic changes of viscera and their relationships. It plays an important role in the theoretical system of TCM and is significant in both expounding the physiology and pathology of the human body and guiding clinical practice. Viscera, which are the basis of the theory of Zangxiang, include the 5 Zang-organs: the heart, lungs, spleen, liver and kidneys. According to the theory of TCM, the lungs open into the nose. The main physiologic functions of the lung are to dominate Qi, control respiration, govern dispersing and descending activities, and regulate water passage. The fact that the nose is the pathway for respiration is why it is believed in TCM that the lung opens to the nose. The 5 Zang organs interact with each other in both the physiologic functions and the pathologic features.

Treatment based on syndrome differentiation is the basic principle guiding clinical diagnosis and treatment of disease. Syndrome is a pathologic generalization of a disease at a certain stage in the course of its development. Since syndrome includes the location, cause and nature of a disease as well as the relation between pathogenic factors and healthy Qi, it reveals the nature of disease more comprehensively and accurately. A patient's symptoms and signs collected with the 4 diagnostic methods are analyzed and generalized, and finally diagnosed with some syndrome or disease. Generally speaking, syndrome is a reflection of waning and waxing of yin and yang of Zangfu-organs or invasion of exogenous evils. Since physiologic functions of every Zang-fu organs are different, the reflections of pathology are different. The theory of physiology and pathology of Zang-fu organs is the theoretical basis of Visceral Syndrome Differentiation.

#### 6.6.2 Syndrome differentiation

According to the theory of TCM, AR falls under the category of

Biqiu. The etiology is based on the deficiency of a healthy-Qi, and external evils take advantage of a weak point. In terms of syndrome differentiation of solid and hollow viscera, AR is induced by the inconsistent function of the lungs, spleen and kidneys, especially because of the deficiency of the kidney-yang. According to the “Standards for the diagnosis and curative effect of Chinese medical symptom” issued by the State Administration of TCM in 1994<sup>266</sup> and *Chinese Otorhinolaryngology* edited by Wang Shizhen,<sup>267</sup> AR is divided into 4 types: kidney-yang deficiency, lung-Qi deficiency, spleen-Qi deficiency, and lung heat.

**Kidney-yang deficiency.** Kidney-yang deficiency and the lung’s suffering from cold can lead to lung-Qi deficiency, which makes the body vulnerable to external evils and causes nasal itching and sneezing. The kidney fails to keep Qi and Qi descends to the top, causing frequent sneezing. Fading life gate fire and Qi transformation failure lead body fluids to ascend to the nose, which triggers constant rhinorrhea. Studies have shown that the kidney plays an important role in the regulation of cAMP/cGMP proportions.<sup>268,269</sup> Pharmacologic studies have found that yang-warming herbal medicinal formulae are instrumental in the IgE regulation system.<sup>270</sup> Seasonal allergic diseases can be prevented by taking the medication in advance, effectively reducing seasonal allergic incidences.

**Lung-Qi deficiency.** The lung-Qi governs the lung and its opening at the nose. If the lung-Qi is deficient, there is insecurity of defense Qi, the lung will suffer from wind-cold evil invasion, and the lung fails to diffuse and descend, which causes stagnation of body fluids, leading to overflow rhinorrhea and Biqiu. Patients often have shortness of breath and fatigue, aversion to wind and cold, pale and fat tongue, thin and pale tongue coating, and weakened pulse. The Wind tends to move and change rapidly by nature, so does the symptoms of AR. The occurrence of lung-Qi deficiency is closely related to AR. Zhao Jiangyun and colleagues<sup>271</sup> have shown that lung-Qi deficiency is related to lower than normal indicators of peripheral T-lymphocyte subpopulation, indicating lower cell immune function of patients, which affects the immune regulation of T cells. It has also been demonstrated that cAMP levels in plasma<sup>272</sup> and nasal secretions<sup>273</sup> are lower in patients with lung-Qi deficiency than in normal subjects. With a decreased cAMP and cAMP/cGMP ratio, the release of chemical medium is strengthened and accelerated, thus affecting the response of the nasal mucosa.

**Spleen-Qi Deficiency.** The spleen is the source of engendering transformation. A healthy spleen is full of Qi and blood, defending the body surface against the invasion of exogenous pathologic factors. When the spleen is deficient, there is no growth of Qi or blood, and leads to lung-Qi deficiency and malnutrition to the nose. Therefore, spleen-Qi deficiency also affects water transportation and regulation, and fluid retention invades nasal orifices, causing nasal mucosal edema and constant rhinorrhea. Moreover, a study has shown that patients suffering from lung-

Qi deficiency and spleen-Qi deficiency have the highest level of serum IgE and a higher proportion of eosinophils in nasal secretions,<sup>274</sup> suggesting that AR is more easily induced by spleen deficiency.

**Lung heat.** Apart from the above-mentioned syndrome differentiation typing, the lung-heat pattern for AR is generally considered one of the most common types.<sup>267,275</sup> As the lung suffers from heat evil, it fails to diffuse and descend, which causes stagnation of body fluids, leading to overflow rhinorrhea. Meanwhile, the heat invades nasal orifices, causing itching and constant sneezing.

## 7. DIAGNOSIS

### 7.1 Diagnosis criteria

#### 7.1.1 Clinical history

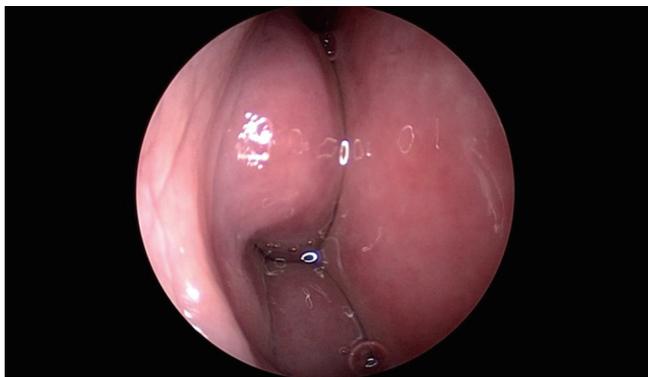
Clinical history is essential for the accurate diagnosis of AR and for the assessment of its severity as well as its response to treatment. The interview begins with a thorough general medical history and should be followed up by questions more specific for allergy including environmental and occupational information. It is also common to collect information on personal and familial histories of patients with allergic disease.

The most frequent symptoms include sneezing, anterior rhinorrhea, bilateral nasal obstruction and nasal pruritus in patients with AR. In addition, most patients with pollen-induced rhinitis have eye symptoms. It is also important to distinguish between allergy and nonallergy symptoms.<sup>56</sup> Subjective assessment of symptoms of AR is generally based on 4 nasal symptoms (sneezing, rhinorrhoea, nasal itching and nasal obstruction) and 2 ocular symptoms (ocular itching/grittiness/redness and ocular tearing).<sup>276</sup> In China, VAS is most commonly used to quantify the above-mentioned assessments.<sup>276</sup>

#### 7.1.2 Nasal examinations

In patients with AR, a nasal examination is necessary. Use of anterior rhinoscopy and nasal endoscopy is the widely used approaches, and nowadays the majority of hospitals in China have been equipped with an endoscopic examination system. Generally speaking, anterior rhinoscopy needs to be paired with the use of a speculum and mirror, and will provide the primary information. Nasal endoscopy is the next step, which is useful for patients with treatment failure or for excluding other conditions.

Nasal examination should describe: 1) the anatomical situation in the nose (*e.g.* the septum, the size of the inferior turbinate, and if possible the structures in the middle meatus); 2) the color of the mucosa; and 3) the amount and aspect of the mucus. An endoscopic image of nasal mucosa in a patient suffering from AR is exhibited in Fig. 12, demonstrating pale and edematous nasal mucosa, watery nasal discharge, and swollen inferior turbinates.



**Fig. 12.** A comprehensive endoscopic image of nasal mucosa suffering from AR.

### 7.1.3 Skin tests

Skin tests are widely used to demonstrate an IgE-mediated allergic reaction in the skin. These tests represent a major diagnostic tool in the field of allergy. As there are many complexities in their performance and interpretation, it is recommended that they be carried out by trained health professionals.<sup>277</sup>

#### 1) Methods

##### a) Skin test methods

Two methods of skin testing, including intradermal skin tests and skin prick tests (SPTs), are available in China. Intradermal skin tests may be employed for allergy diagnosis in some instances (e.g. weak allergen solution). They are not widely used because they correlate less well with symptoms.<sup>278</sup> Additionally, they may induce some false-positive reactions and systemic reactions.<sup>279,280</sup> SPTs are recommended for the diagnosis of immediate-type allergy because there is a high degree of correlation between symptoms and provocative challenges as recommended by the Position Papers of the European Academy of Allergology and Clinical Immunology (EAACI),<sup>281</sup> WHO,<sup>282</sup> and the US Joint Council of Allergy Asthma and Immunology.<sup>283,284</sup> In accordance with this recommendation, SPTs have also been widely used in China since 2000 to 2010. The inhaled antigens tested include HDMs (*Der f* and *Der p*), seasonal grass pollens (giant ragweed, mugwort, lamb's quarters, *Humulus*, *Chenopodium album*), animal hair (dog and cat), mold (indoor and outdoor mustiness or floricultural environment) and cockroach. Due to the Food and Drug Administration policy restrictions concerning foreign SPT diagnostic reagents, few domestic SPT diagnostic reagents are currently used for allergen identification.

##### b) Negative and positive control solutions

Due to inter-patient variability in skin reactivity, it is necessary to include negative and positive controls in every skin test. Negative control solutions are diluents used to preserve allergen vaccines. The rare dermographic patient will produce wheal-and-erythema reactions to the negative control. Any reaction at the negative control test site will hinder the interpretation of the

allergen site.<sup>283</sup> Positive control solutions are used to detect suppression by medications or disease and to determine variations in technician performance. The usual positive control for prick-puncture testing is histamine dihydrochloride.<sup>285,286</sup>

#### 2) Criteria of positivity

Skin tests should be read at the peak of their reaction by measuring the wheal and the flare approximately 15 minutes after performance of the tests. For prick tests, when the control site is completely negative, wheals of > 3 mm represent a positive skin response.<sup>287,288</sup>

#### 3) Factors affecting skin testing

Skin reaction is dependent on a number of variables that may alter performance of the skin tests. The quality of the allergen extract is of importance. If possible, standardized allergens should be used.<sup>281</sup> Drugs may also affect skin tests, and it is therefore always necessary to ask the patient questions about the drugs they have taken. This is particularly the case for oral H<sub>1</sub>-antihistamines. Montelukast neither appears to reduce skin test reactivity<sup>289,290</sup> nor needs to be discontinued before skin testing.

### 7.1.4 Serum specific IgE measurements

In contrast to the low predictive value of total serum IgE measurements in the diagnosis of allergic diseases, the measurement of allergen-specific IgE in serum is of importance. Furthermore, specific IgE measurements are not influenced by drugs or skin diseases.

#### 1) Methods

The first technique ever used to accurately measure serum-specific IgE was the radioallergosorbent test (RAST).<sup>291,292</sup> New techniques are now available using either radio- or enzyme-labelled anti-IgE.<sup>293,294</sup> Enzyme-labelled anti-IgE measurement has been widely used in China. Results are expressed in terms of units of IgE (IU/mL, KU/L). ImmunoCAP system (Pharmacia, Uppsala, Sweden) and Euroline Allergy Diagnostics (Beijing Oumeng Biotechnology Co., Ltd., Beijing, China) are currently the most widely used manufacturers in China. The assay spectrum of Euroline comprises different profiles guided by diagnostic requirements (food, inhalation and pediatric allergy) with up to 54 parameters tested in one determination, basically meeting the needs of the inhaled allergens for AR diagnosis. In comparison, ImmunoCAP has only finished the registrations of 30 allergens, which involved total IgE, phadiatop, food, indoor inhaled allergens and a portion of outdoor pollens, thereby greatly limiting its application in China.

#### 2) Criteria for positivity

The IgE level above 0.35 KU/L is usually testified as a positive result. However, some sensitized subjects have an IgE level below this cutoff, and the measurement of serum specific IgE is

usually less sensitive than SPTs.<sup>295</sup> Although a low specific IgE titer may not be clinically relevant, the titer of serum specific IgE is usually unrelated to the severity of symptoms.

### 3) Screening tests using serum specific IgE

Some methods use either a mixture of several allergens in a single assay<sup>296</sup> or test several different allergens during a single assay.<sup>297</sup> These tests can therefore be used as screening tests for the diagnosis of allergic diseases. Certainly, using most of these tests, the patient is defined only as allergic or nonallergic and more extensive investigations for rhinitis are needed if the test is positive.

#### 7.1.5 Imaging

Computerized tomography (CT) is the principal radiologic investigation for most sinonasal disorders, but it is of limited use in the diagnosis of AR.<sup>298-302</sup> CT scans should be carried out only in the following instances: to exclude other conditions, in patients who do not respond to treatment, and in patients with unilateral rhinitis.

#### 7.1.6 Nasal provocation tests (NPTs)

NPTs elicit a response from the nasal mucosa by controlled and standardized exposure to allergens. Interpretation of nasal response includes symptom assessment and nasal patency evaluation. Rhinomanometry and acoustic rhinometry, 2 widely used complementary techniques, can evaluate nasal patency objectively.<sup>303</sup> To date, NPTs are mostly used in research and seldom in clinical practice in China due to the lack of the registered drugs for NPTs. Additionally, they are important in the diagnosis of occupational AR and sometimes performed before immunotherapy for AR.<sup>304,305</sup>

#### 7.1.7 Fractional exhaled NO

Fractional exhaled NO (FeNO) can be used as a reproducible and noninvasive biomarker for asthma and other lower respiratory diseases.<sup>306,307</sup> The possible use of nasal NO measurements in the diagnosis and treatment of AR still needs to be further evaluated because of variable as well as contradictory findings of nasal NO concentrations in this disease.<sup>308-310</sup> Likewise, nasal NO test was carried out in China in just recent years as there was not enough consistency in available data to obtain the range of normal value, which is necessary for the diagnosis of AR or other upper airway inflammatory diseases.<sup>311-314</sup>

#### 7.1.8 Diagnosis of AR in TCM

TCM employs unique methods for the diagnosis of AR, which are completely different from those employed in Western medicine. Looking, listening, questioning and feeling the pulse are the 4 main ways of diagnosing AR, by determining 4 types of syndromes for AR as detailed above in section (6.6.2) on “*Syndrome Differentiation*”.

## 7.2 Differential diagnosis

Differential diagnosis of AR is broad and somewhat complex. Inflammation of nasal mucosa and the symptoms of sneezing, itching, rhinorrhea and nasal congestion need to be identified appropriately based on a careful history and targeted examinations.

### 7.2.1 Vasomotor Rhinitis

Vasomotor rhinitis, also known as nonallergic rhinitis and idiopathic rhinitis, is rhinitis with an unclear etiology, which may possibly be associated with neuroendocrine dysfunction.<sup>315,316</sup> The symptoms of vasomotor rhinitis, particularly sneezing and watery rhinorrhea, can be induced typically by cold air, irritant odors, tobacco smoke, alcohol, sports and emotional reaction.<sup>317</sup> There is no unique finding with tests for sensitization to allergens and eosinophil granulocyte in nasal secretions.

### 7.2.2 Nonallergic rhinitis with eosinophilia syndrome (NARES)

NARES is a clinical syndrome characterized by hypereosinophilia. Patients may exhibit similar symptoms to AR, but more serious and often associated with olfactory dysfunction.<sup>318</sup> Allergen sensitization tests and nasal provocation tests are negative. Hypereosinophilia is notable both in nasal discharge and blood, with the estimated standards showing >20% more eosinophils than granular cells and monocytes in the nasal discharge and >5% eosinophils in peripheral blood.<sup>317</sup>

### 7.2.3 Infectious rhinitis

Infectious rhinitis is caused by a viral or bacterial infection over a short course of 7-10 days and presents with similar symptoms compared to AR initially, accompanied by fever, headache, weakness and limb pain.<sup>319</sup> Tests for sensitization to allergens and eosinophils in nasal secretions are negative, but high lymphocyte counts are noted after acute bacterial infection.<sup>320</sup>

### 7.2.4 Hormonal rhinitis

Hormonal rhinitis may typically presents nasal congestion and rhinorrhea caused by abnormal levels of endocrine hormones including sex hormones, thyroxine and pituitary hormones. Tests for sensitization to allergens and eosinophils in nasal secretions are negative.

### 7.2.5 Medicamentous rhinitis (*Rhinitis medicamentosa*)

Nasal congestion caused by long-term use of a decongestant nasal spray is the marked feature of medicamentous rhinitis. Tests for sensitization to allergens and eosinophils in nasal secretions are negative.<sup>321</sup>

### 7.2.6 Aspirin intolerance triad

Rhinitis symptoms are accompanied with asthma and nasal polyps, perhaps with urticaria and angioedema provoked by acetylsalicylic or other analgesics. Nasal polyps with high recur-

rence and uncontrolled asthma are the challenges. Positive aspirin provocation test, identified history, hypereosinophilia and negative allergen sensitization test are the identified features.<sup>322</sup>

### 7.2.7 Cerebrospinal fluid rhinorrhea

Physicians should be alert to significant trauma history, watery rhinorrhea, and absence of itching and sneezing in the diagnosis of cerebrospinal fluid leaks.<sup>323,324</sup>

Rarely, nasal symptoms similar to those of AR can also occur as a consequence of a foreign body<sup>325</sup> or nasal tumor.<sup>326</sup> A detailed history and examinations are the key to differential diagnosis of this condition.

## 7.3 QOL measurements

Rhinitis severity is based on the impact of disease on QOL. QOL measurements are the best approximation of the burden of disease on the patient with AR, particularly as a quantifiable measure of a patient's perception of the impact of his/her disease and its treatment on his/her daily life, physical/psychological/social functioning and general well-being.<sup>69,327</sup> QOL appears to be moderately correlated with the more classic outcome variables used in clinical trials, such as daily symptom scores and nasal hyperreactivity. The effect of AR on QOL also runs parallel with the effect on conventional medical outcome measures. Generic or disease-specific questionnaires estimate QOL and are widely used both in clinical practice and in research. The choice of questionnaire should depend on the task at hand. The findings of different specific instruments of questionnaire can be combined for scheduled purpose.

### 7.3.1 Generic QOL questionnaire

Generic QOL questionnaires are used to measure physical, mental and psychosocial functions in all health conditions, and allow comparisons between different diseases and health populations. The most widely tested and used instrument for AR is Short-Form 36-item health survey questionnaire (SF-36), which provides summary scores in 2 domains: physical health and mental health.<sup>7</sup> This questionnaire allows comparisons between different diseases and health populations, which makes them less suitable for measuring individual specific clinical outcomes.<sup>327</sup> A Chinese version of SF-36 has been widely used in evaluation the QOL of adult AR and is especially suitable for comparison with other diseases. (The Chinese version of SF-36 is shown in *Supporting information 1*).

### 7.3.2 Disease-specific QOL questionnaires

Specific instruments have been designed for assessing problems patients experience from AR or conjunctivitis, and have the advantage of describing the disease-associated problems of the patients more accurately.<sup>7</sup>

**Table 6.** Different versions of RQLQ for different age groups

Questionnaire	Application	Number of Item	Domains
RQLQ	Adult	28	Sleep Non-hay fever symptoms Practical problems Nose symptoms Eye symptoms Activities Emotional function
PADQLQ [329]	Children 6 to 12 years old with SAR	23	Nose symptoms Eye symptoms Practical problems Other symptoms Activities
RQLQ for Adolescents [330]	12- to 17-year-old adolescents	25	Sleep Emotions Nose symptoms Eye symptoms Other hay fever symptoms Non-hay fever symptoms

RQLQ, The Rhinoconjunctivitis Quality of Life Questionnaire; PADQLQ, The Pediatric Allergic Disease Quality of Life Questionnaire.

#### 1) Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

The RQLQ has been employed as a gold standard instrument of QOL in adult patients with both AR and rhinoconjunctivitis, and is widely used to assess the symptoms and effects of therapy.<sup>328</sup> The RQLQ contains a list of 28 health-related items in 7 domains including sleep, non-hay fever symptoms, practical problems, nose symptoms, eye symptoms, activities and emotional function (Table 6). The RQLQ has also been adapted specifically for pediatric patients (PADQLQ)<sup>329</sup> and adolescent patients<sup>330</sup> according to health-related items and domains particularly relevant to these groups of patients (Table 6). The Chinese version of RQLQ is now available and can be acquired by authorization from Juniper (Shown in *Supporting information 2*). Currently, RQLQ is widely used in the clinic and for research purposes, especially to assess the effects of therapy including drug therapy and allergen immunotherapy.

#### 2) Other forms of the RQLQ

Different versions of the RQLQ have been developed for special purposes. The Standardized Version of the RQLQ (RQLQ(S)) was developed by replacing the 3 "patient-specific" activity questions of RQLQ with generic activities (regular activities at home and at work, social activities and outdoor activities) to provide better evaluation for activities.<sup>331</sup> The Mini RQLQ, which contains only 14 questions, was developed particularly for large clinical trials.<sup>332</sup> The Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ) was designed to measure the functional problems that are most troublesome to patients with nocturnal AR. The NRQLQ consists of 16 items over 4 domains (sleep

problems, symptoms during sleep time, symptoms on waking and practical problems).<sup>333</sup>

#### 7.4 Psychologic status evaluation

Psychologic status is evaluated by the Self-reporting Inventory, which has been recognized as having satisfactory reliability, validity and utility. Psychologic status evaluation methods can be divided into 2 sides, which involve mental health evaluation and personality tests.

Mental health evaluation has been widely applied in the field of clinical medicine and includes the following items:

- 1) SCL-90 is one of the most famous psychologic measuring scales. It is sourced from the Cornell Medical Index and is widely used in psychiatric departments and psychologic counselling clinics. SCL-90 includes somatization, compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic disorder, paranoid personality and psychosis. Although Symptom Checklist-90 (SCL-90) can reflect the patient's mental health dimension relatively comprehensively, it is not a diagnostic tool, but just a type of screening checklist.
- 2) Self-rating Depression Scale (SDS) and Self-rating anxiety Scale (SAS) are specific screening checklists for assessing the patient's subjective feeling of depression and anxiety, respectively. In addition to early screening of patients suffering from depression and anxiety, these screens can also be used to observe changes in the degree of severity and development of the state of the illness during therapy.
- 3) State-Trait Anxiety Inventory (STAI) can not only directly reflect the level of the anxiety of patients, but also distinguish the state of anxiety from the consistent trait anxiety, thus offering the precise direction for further intervention and treatment.
- 4) Hospital Anxiety and Depression Scale (HADS) is suitable for rough screening of the tendency for depression and anxiety among general patients.

The common personality tests involve the following 2 categories:

- 1) Minnesota Multiphasic Personality Inventory (MMPI) is as a diagnostic tool in psychiatry for assessing personality disorder and can fully reflect the degree of subjects' physical and mental dimensions as well as clinical symptoms. MMPI covers 2 parts: 4 validity scales and 10 clinical scales. The validity scales include Question (Q), Lie scale (L), Infrequency (F) and Correction (k), while the clinical scales involve Hypochondriasis (Hs), Depression (D), Hysteria (Hy), Psychopathic deviate (Pd), Masculinity/femininity (Mf), Paranoia (Pa), Psychasthenia (Pt), Schizophrenia (Sc), Hypomania (Ma) and Social introversion (Si).
- 2) Eysenck Personality Questionnaire (EPQ) is a type of simplified personality inventory test that has been categorized in terms of 3 personality dimensions, which involve intro-

version-extroversion, psychoticism and nervousness, and exert a great effect on the outcome of the treatment for long-term chronic diseases and tumors.

All the above-mentioned mental assessment scales are in Chinese and can be found at <http://www.bnuftr.com/ceping/test>. The physician should issue the username and password to subjects completing these assessment scales.

## 8. TREATMENT

### 8.1 Therapeutic strategy

The therapeutic principle of AR involves a comprehensive approach including environmental control, pharmacotherapy, AIT and patient education.<sup>7</sup>

These 4 key elements combine the prevention and treatment of AR. As an important part of prevention and treatment strategy, environmental control should focus on avoidance or reduction of various allergens as well as air pollutants; however, existing measures are often difficult to achieve complete control of AR. Pharmacotherapy and AIT are the main treatments for AR. Although AR is currently not completely curable, standardized comprehensive therapy can achieve optimal symptom control and significant improvement in the QOL of patients.<sup>334</sup> Individualized approach to the education of the patient, as well as disease management and follow-up, appears to be of importance.

### 8.2 Allergen avoidance

Individuals exposed to high concentrations of indoor allergens (*e.g.* HDMs and animal dander) may benefit from multifaceted avoidance measures after environmental counseling.<sup>7,333</sup> A Cochrane systematic review has shown that house dust mite avoidance measures can reduce allergen load and improve symptoms of perennial AR.<sup>335</sup> However, the authors of this review concluded that due to the small sample size of clinical trials and the poor quality of the evidence, it is still difficult to provide precise recommendations. A Chinese multicenter, randomized, placebo-controlled, crossover study has demonstrated that pollen blocker cream is effective in relieving nasal symptoms and improving QOL in both adults and children with perennial AR due to HDM.<sup>336</sup> Moreover, a systematic review and meta-analysis suggests that interventions to prevent and remediate indoor dampness and mold may reduce the risk of AR.<sup>337</sup>

During outdoor activities in season with a high load of pollens, patients sensitive to pollen should avoid the peak of allergenic pollens spread in the air to reduce AR symptoms attack.

For individuals exposed to pollens in a natural environment, we recommend some allergen-controlling tools (*e.g.* special masks, glasses, nasal filters, pollen blocker cream, nasal cellulose powder), which can reduce nasal inhalation or conjunctival contact of the allergenic pollen and relieve nasal and ocular symptoms.<sup>7,338-341</sup>

### 8.3 Pharmacotherapy

#### 8.3.1 H<sub>1</sub>-antihistamines

A large number of H<sub>1</sub>-antihistamines have been available worldwide since 1942 when the antihistamines were introduced for clinical applications for the first time. Antihistamines act as inverse agonists that combine with and stabilize the inactive conformation of the H<sub>1</sub>-receptor, shifting the equilibrium toward the inactive state. Antihistamines are functionally classified into 2 groups, first- or second-generation antihistamines, according to whether or not they enter the blood brain barrier (BBB) readily. First-generation antihistamines can cross the BBB readily and also have anticholinergic effects, which limits their use as a consequence of the side effects of sedation and mucosal dryness.<sup>342</sup>

##### 1) Oral antihistamines

Oral antihistamines are effective against nasal symptoms, particularly rhinorrhea, sneezing and nasal itching, which are mainly mediated by histamine, but are less effective against nasal congestion.<sup>343</sup> First-generation antihistamines often cause adverse effects such as sleepiness, impaired performance and dry mouth. In contrast, second-generation antihistamines are effective to some extent for nasal congestion aside from sneezing and watery rhinorrhea, and also cause less adverse side effects. Thus, in almost all situations, the use of oral second-generation antihistamines is proposed as first-line therapy for intermittent and persistent AR.<sup>7</sup> Commonly used second-generation antihistamines include cetirizine, loratadine, levocetirizine and desloratadine. Some of these are marketed as OTC medications.

These agents have a rapid onset of action, occurring from 1 to 2 hours after oral administration. Most of them have duration of action of more than 24 hours, and patients can take them once daily. During regular daily dosing, little or no tolerance occurs towards their effects and they can also relieve some symptoms of eyes.<sup>344</sup>

The clinical effect for the control of nasal symptoms in trials of intermittent allergic rhinitis lasting 2 weeks and of persistent allergic rhinitis lasting 4 weeks has been extensively demonstrated; however, the sample-size has usually been small.<sup>345</sup>

The use of second-generation antihistamines prior to pollen exposure can improve nasal symptoms and activity impairment in pollinosis. Treatment is better on a regular basis than on as-needed basis for symptom relief.<sup>344</sup>

In contrast to first-generation antihistamines, second-generation antihistamines are relatively safe. The long-term safety of second-generation antihistamines, including cetirizine, levocetirizine, fexofenadine, loratadine and desloratadine, have been validated in randomized controlled trials (RCTs) lasting 6 to 18 months, in both adults and in children as young as 1 to 2 years old.<sup>342,343,346</sup> Currently, numerous oral antihistamine products are available for use in Chinese AR patients (Table 7).

**Table 7.** Market share of the main oral antihistamine products used in China

Product	Component	Side effect	Market ratio (%)
ZYRTEC and Chinese analog	Cetirizine	Slight sedation	8
KAISITING	Ebastine	Slight sedation	10
CLARITYNE and Chinese analog	Loratadine	Slight sedation	12
ENLISI and Chinese analog	Desloratadine	Minor sedation	12
XYAL and Chinese analog	Levocetirizine	Minor sedation	8
BEIXUE	Desloratadine Citrate Disodium	Minor or no sedation	31
LUSU	Rupatadine	Minor or no sedation	1

##### 2) Intranasal antihistamines

Intranasal antihistamines are also proposed as first-line therapy. The intranasal preparations are targeted delivery that can increase dosage to nasal tissues while decreasing systemic effects.<sup>347</sup> Intranasal antihistamines have a more rapid onset of action than oral antihistamines, ranging from 15 to 30 minutes versus 150 minutes of average onset time. Due to the rapid onset of action and targeted delivery of intranasal formulations, they are especially useful in patients with episodic nasal symptoms or as a pretreatment before inhaled allergen exposure.<sup>348</sup> However, because of washout from the nasal mucosa, intranasal formulations require administration at 6 to 12 hours intervals.

Intranasal antihistamines also have the advantage for the relief of nasal congestion, which is much more efficacious than oral preparations. Intranasal administration shows benefit even in patients who fail oral treatment. A recent meta-analysis has shown that the efficacy of intranasal antihistamines was superior to that of oral antihistamines with respect to total nasal symptom scores (TNSS), and there was no significant difference in TNSS between patients treated intranasal antihistamine and those treated with intranasal corticosteroids.<sup>349-351</sup>

Currently, only 4 intranasal antihistamine products (AZEP, MIN QI, LIVOSTIN and SHUNTUOMIN) are available for the treatment of AR patients in China, of which AZEP (azelastine hydrochloride) has the largest share of the Chinese market (Table 8). In a multicenter, randomized, double-blind, parallel-group trial, Han and colleagues<sup>352</sup> have demonstrated that azelastine and levocabastine nasal sprays, which are commonly used worldwide for the treatment of AR, are comparably safe and effective in the treatment of Chinese patients with moderate-to-severe persistent AR.

The most common adverse events related to intranasal formulations use are local side effects such as epistaxis/nasal burning, poor taste, sedation, more frequent dosing and increased cost relative to oral formulations. Although the incidence of side ef-

**Table 8.** Intranasal antihistamine products available in China

Product	AZEP	MIN QI	LIVOSTIN	SHUNTUOMIN
Component	Azelastine hydrochloride	Azelastine hydrochloride	Levocabastine Hydrochloride	Sodium Cromoglicate, Naphazoline hydrochloride and Chlorphenamine Maleate
Age	>6 years	>12 years	Not suitable for <12 years	>7 years
Manufacturer	Meda, Germany	Guizhou Yunfeng, China	Janssen Pharmaceutica NV, USA	Shandong Tianshun, China
Side effect	Bitter	Dozy	Dozy, renal insufficiency need to follow physician's advice	Dozy
Market ratio	53.65%	27.12%	14.23%	5%

fects is low, caution should be exercised at the initiation of intranasal antihistamines for signs of adverse events, and follow-up with a clinician is advised to assess response and side effects.

### 8.3.2 Leukotriene receptor antagonists

Leukotrienes are among the major mediators that are involved in the pathogenesis of AR and act by attracting eosinophils, increasing microvascular leakage and elevating mucous gland secretion.<sup>353</sup> Leukotriene modifiers include leukotriene synthesis inhibitors and leukotriene receptor antagonist (LTRA). Singulair (Montelukast from MSD) is the patient's favourite choice of the LTRA products and occupies 11.7% of the total market in China (data taken from IMS CHPA (<http://www.imshealth.com>)).

Montelukast works by blocking the leukotriene receptor and thus blocks the end organ response of leukotrienes. Montelukast has been shown to improve both allergen-induced nasal and ocular symptoms<sup>354</sup> and early intervention with montelukast before pollen season significantly improves AR symptoms, compared to post-onset treatment with topical steroids only.<sup>355</sup> Furthermore, LTRA is better suited for night-time symptoms and contributes to improvements in sleeping disorders.<sup>356</sup>

Compared to non-sedating antihistamines, LTRAs tend to provide more relief of nasal congestion. However, a meta-analysis by Xu and colleagues<sup>357</sup> comparing the efficacy and safety of selective antihistamines and LTRAs for the treatment of seasonal AR, and a clinical trial by Liu and colleagues<sup>358</sup> comparing the effect of treatment with montelukast or loratadine in patients with AR indicated that antihistamines and LTRAs had similar effects for seasonal AR. Indeed, a combined use of montelukast and loratadine has been suggested to provide the most effective treatment for seasonal AR and associated eye symptoms.<sup>353</sup> Furthermore, the addition of an antihistamine to montelukast is reported to be equivalent to intranasal corticosteroids (INS).<sup>354</sup> Montelukast in combination with intranasal steroids has also been shown to obtain faster improvement in TNSS,<sup>359</sup> and in AR patients with steroid resistance LTRA can be used as an adjunct therapy.<sup>360</sup>

Montelukast 5 or 10 mg once daily has been reported to be a well-tolerated and safe therapeutic option for children. Alternative forms such as liquids or oral disintegrating tablets are available. Montelukast is pregnancy category B medication, allow-

ing ease of administration to pregnant woman.

LTRAs constitute good therapeutic options in AR, with acknowledged underlying mechanisms,<sup>361</sup> and are thus likely to provide greater benefits to AR patients in clinical practice in China.

### 8.3.3 Nasal corticosteroids

INS is the most efficacious anti-inflammatory medications available for the treatment of AR.<sup>362</sup> The choice of INS in the treatment of AR is due to the attainment of high drug concentrations in the local mucosa, with a fairly small risk of systemic adverse effects.

INSs directly modulate the pathophysiology of AR, as they have been shown to significantly inhibit recruitment of basophils, eosinophils, neutrophils and mononuclear cells to nasal secretions in nasal allergen challenge models.<sup>363-365</sup>

One recent study has indicated that INS delivered 86% of metered dose to the nasal cavity, with approximately 60% of metered dose to the posterior nasal cavity.<sup>366</sup> These delivery characteristics contributed to sustained nasal contact time, which improved the outcomes. For seasonal AR patients, inflammatory cells and cytokines within the nasal mucosa and secretions have been shown to be significantly reduced after use of INS.<sup>367,368</sup> Similarly, INSs tend to decrease the SP concentration in tears of patients with seasonal AR, which is correlated with the severity of ocular and nasal symptoms.<sup>369</sup> The efficacy of INS appears after 3-5 hours of dosing, but maximum efficacy may develop over a period of up to 2 weeks.

INS has proved to be effective in improving all symptoms of AR.<sup>370</sup> If nasal congestion is present or symptoms are frequent, INS is the most appropriate first-line treatment as it is more effective than any other treatment.<sup>371</sup> INS is not only effective for all nasal symptoms, but also for ocular symptoms, including itching, tearing, redness and puffiness, with no significant difference compared to intranasal antihistamine.<sup>372</sup>

High drug concentrations of INSs can be achieved at receptor sites in the nasal mucosa, with a minimal risk of systemic adverse effects, in the treatment of AR. An efficient topical delivery system also ensures fewer systemic side effects and leads to a better treatment result, which benefits the AR patient significantly. INSs are well tolerated and the adverse effects are few in number. Safety and efficacy are proved for all INSs available by

Table 9. INSS available in China

INS	Onset of action	Receptor affinity	Minimum age	Recommended dosage	Patients' preference	Safety
Mometasone furoate	In subjects with SAR, mometasone-furoate nasal spray significantly improved nasal symptom scores compared with placebo, in as little as 7 hours after a single 200 µg dose and total symptom scores as soon as 5 hours	2,244	2 years	Adults and children > 12 years of age: 2 sprays (100 µg) per nostril q.d. Children 3-11 years of age: 1 spray (50 µg) per nostril q.d.	> Fluticasone propionate	Good
Mometasone furoate (Generic)	N/A	N/A	3 years	Adults and children > 12 years of age: 2 sprays (100 µg) per nostril q.d. Children 3-11 years of age: 1 spray (50 µg) per nostril q.d.	N/A	Good
Triamcinolone acetonide	1-2 days	233	6 years	Adults and children > 12 years of age: 2 sprays (110 µg) per nostril q.i.d. Children 6-12 years of age: 1 spray (55 µg) per nostril or 110 µg q.i.d., up to 2 sprays (110 µg each) per nostril or 220 µg q.d.	N/A	Good
Budesonide		855	6 years	Adults and children > 6 years of age: 1 spray (32 µg/spray) per nostril q.i.d. up to a maximum of 256 µg/day (> 12 years of age) or 128 µg/day (6 to < 12 years of age)	N/A	Good
Fluticasone propionate		1,775	4 years	Adults: 2 sprays (100 µg) per nostril q.i.d. or 1 spray (50 µg) b.i.d. Adolescents and children > 4 years of age: 1 spray (50 µg) per nostril per day up to, but not in excess of, 2 sprays (100 µg) per nostril per day	< Mometasone furoate	Good
Beclomethasone dipropionate	N/A	1,345	6 years	Adults and children > 12 years of age: 1 or 2 sprays (42-84 µg) per nostril b.i.d. (total dose 168-336 µg/day) Children 6-12 years: 1 spray (42 µg) per nostril b.i.d. for total of 168 µg/day up to 2 sprays per nostril b.i.d. for total of 336 µg/day	N/A	Good

multiple studies, with the side effects being mild in severity and similar in incidence as for placebo.

Currently, only 2 clinical trials investigating the effects of INS in Chinese subjects have been published in international peer-review journals. Zhang and colleagues<sup>373</sup> assessed the effect of mometasone furoate nasal spray 200 µg once daily in a multicenter open-label study involving 500 patients with moderate-to-severe AR. The authors reported that mometasone furoate nasal spray reduced symptoms and improved quality of life of the patients. Han and colleagues<sup>374</sup> also assessed the effect and safety of fluticasone furoate nasal spray 110 µg once daily or placebo in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study involving 363 adult and adolescent subjects with intermittent or persistent AR. The authors reported that fluticasone furoate nasal spray was safe and significantly more effective than placebo in improving nasal symptoms as well as in decreasing rhinoscopy score and activities of daily living (ADL) score in patients with intermittent or persistent AR. Currently, however, fluticasone furoate nasal spray is not in general clinical use in China.

Currently, there are 4 multinational corporation and 4 domes-

tic corporation INS products in clinical use in China, of which the multinational corporation (MNC) INS have 85% of the market share, compared to only 15% of the market share for domestic INS. Nasonex continues to be the No. 1 product among China INS market. All data are from IMS China Hospital Pharmaceutical Analysis (CHPA) (<http://www.imshealth.com>). Table 9 exhibits the main characteristics of the INSS available in China.

#### 8.3.4 Mast cell stabilizers

Mast cell stabilizers can stabilize the membrane of mast cells and basophils to prevent degranulation, thereby inhibiting the release of a variety of proinflammatory mediators, including histamine. The mast cell stabilizers are commonly used in clinical practice and include cromolyn sodium, tranilast, pemirolast potassium and so on. In China, tranilast is more widely used. These drugs partly relieve the symptoms of nasal itching, sneezing and rhinorrhea, but are not very effective in controlling nasal obstruction. In AR patients with allergic conjunctivitis, cromolyn sodium eye drops can improve ocular symptoms. Based on the mechanism of action of the mast cell stabilizers, these drugs can be used as prophylactic treatment. Indeed, patients

with pollinosis (seasonal AR) are usually required to use mast cell stabilizers for about 2 weeks before the spread of pollen to reduce nose and eye symptoms.<sup>8,375</sup>

Although mast cell stabilizers have good safety and tolerance, they belong to second-line drugs<sup>376</sup> because they have some limitations such as slow onset and short action, and also because they may not be effective in the treatment of existing symptoms.

### 8.3.5 Nasal decongestants

Topical decongestants can constrict blood vessels in the nasal mucosa and improve nasal patency, thus relieving the symptom of nasal obstruction in patients with AR. In clinical therapy, the most frequently used nasal decongestants are ephedrine hydrochloride, pseudoephedrine hydrochloride, oxymetazoline hydrochloride, xylometazoline hydrochloride and so on. In China, the commonly used nasal decongestant is 0.05% oxymetazoline. It has been shown that the clinical concentration of 0.05% oxymetazoline has no obvious inhibitory effects on human nasal ciliary beat frequency *in vitro*<sup>377</sup>; however, it should be highlighted that the nasal decongestants relieve the symptom of nasal congestion only temporarily in AR patients. When used in conjunction with INS, decongestants can benefit AR patients with stuffy noses by improving even and effective distribution of the INS.<sup>4,378</sup>

It has been pointed out that topical decongestants can cause rebound nasal congestion after continuous use for 5 days and drug-induced rhinitis after long-term use, and pose a risk to fluctuating blood pressure in elderly patients.<sup>379</sup> As drugs belonging to a second-line therapy, nasal decongestants are generally not used continuously for more than 7 days.<sup>376</sup> It is important to remember that a lower dose (half the concentration of the drug for adults) of nasal decongestant spray should be chosen for children.<sup>380</sup>

Oral decongestants could cause systemic side effects including hypertension, myocardial ischemia, arrhythmia and tachycardia, and are therefore not recommended for the treatment of AR patients.

### 8.3.6 Nasal anticholinergics

Intranasal anticholinergics can inhibit both watery secretion of nasal glands and vasodilatation of airway blood vessels. They are recommended as second-line drugs.<sup>376</sup> Ipratropium bromide, a quaternary derivative of isopropyl noratropine, has proved to be effective in controlling watery nasal discharge of AR patients.<sup>7</sup> Currently, however, there is no approved intranasal anticholinergic in the Chinese market.

Although systemic side effects of nasal anticholinergics are rare, care should nevertheless be exercised when these drugs are prescribed to patients suffering from prostatic hypertrophy or glaucoma.<sup>376</sup>

### 8.3.7 Nasal saline irrigation

Nasal saline irrigation (NSI) is a simple and inexpensive treatment for AR as well as other nasal disorders (*e.g.* CRS and atrophic rhinitis). Several studies have demonstrated NSI to be effective. In China, numerous types of irrigation equipment are available, and a patented product of nasal irrigation has recently been developed and extensively used by Beijing TongRen Hospital as shown in Fig. 13.

The exact mechanism underlying the efficacy of NSI is not well understood, but at least 3 have been proposed. First, NSI has a direct cleaning effect. As the saline passes through the nasal cavity, it can humidify and remove obstructive mucus and crusts. This can likely improve the sense of breathing immediately. Secondly, NSI can remove or reduce the inflammatory mediators and allergenic proteins such as histamine, prosta-



**Fig. 13.** Nasal irrigation equipment developed and patented by Beijing Tongren Hospital. (A) Nasal irrigator and salt package. (B) A patient performing nasal irrigation.

glandins, leukotrienes, eosinophil-released major basic protein and pollen. Thirdly, NSI can restore impaired nasal mucociliary function. Improved mucociliary clearance with increased ciliary beat frequency has been shown in patients receiving nasal rinsing.<sup>381-385</sup>

Furthermore, NSI may improve the efficacy of topical medications, such as INS and intranasal antihistamines, via clearing excessive nasal secretions and decreasing pre-existing edema. It is crucial that NSI is proposed as a good adjunctive treatment option to maintain the effectiveness of other treatment, particularly in children and pregnant women.<sup>386</sup>

### 8.3.8 Chinese herbal medicines

Treatment based on syndrome differentiation, an important feature of TCM, is the basic principle guiding clinical diagnosis and treatment of disease. According to the theory of Zangxiang, the treatment of AR emphasizes syndrome differentiation. TCM in the treatment of "AR" involves "Toning" the kidney, thus benefiting the lung and invigorating the spleen simultaneously. The kidney can fully play the controlling and astringing role by nourishing kidney and invigorating yang, and therefore bring sneezing to a halt. The transportation and transformation function of the spleen is strengthened; therefore, the Qi and blood are vigorous. With adequate lung-Qi and firm interstitial striae, the body surface is protected from the invasion of exogenous pathologic factors such as wind evil. Therefore, AR can be effectively prevented.

The treatment of the kidney-yang deficiency involves warming yang and invigorating the kidney; commonly used formulas are Jin Gui Shen Qi Wan and You Gui Wan. Sun and colleagues<sup>387</sup> adopted YouGui Soup to treat AR with kidney-yang deficiency and showed that YouGui treatment had a remarkable effectiveness on symptoms, and the total effective rate was 89.4%.

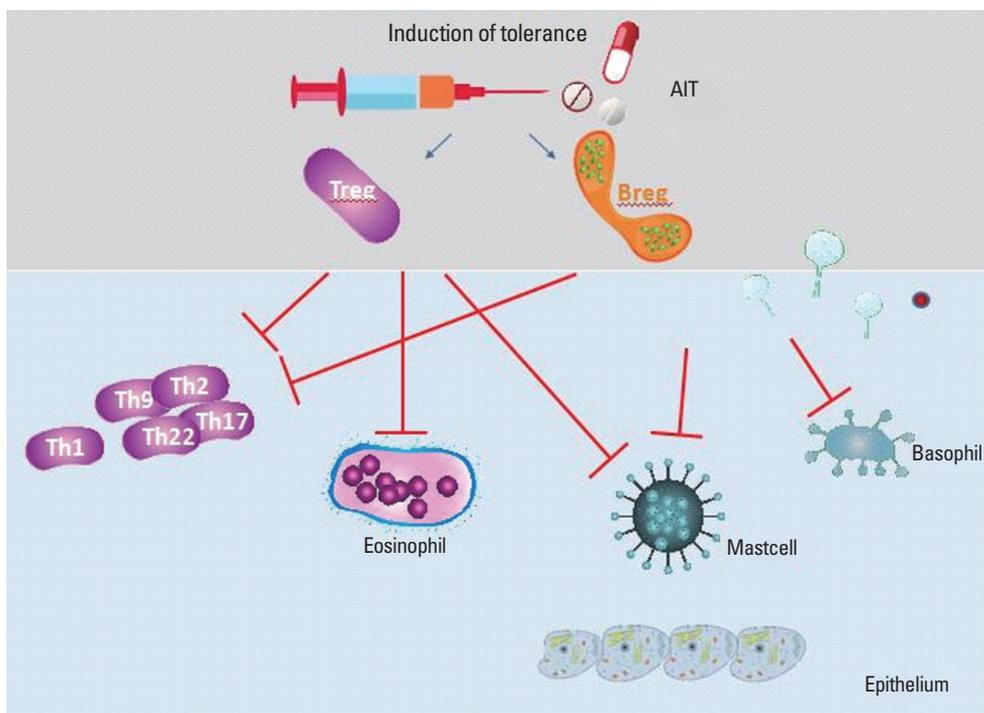
The treatment of lung-Qi deficiency involves warming the lung to dissipate cold. The common prescriptions are Xiao Qing Long decoction, Guizhi decoction and Yupingfeng granule, Cangerzi granule, *etc.* Lin and colleagues<sup>388</sup> used the method of invigorating Qi to consolidate the exterior to treat AR, adjusting cyclic nucleotide levels in the body, inhibiting IgE and mast cell degranulation, and restoring blood flow in nasal mucosa. This suggests invigorating Qi and benefiting the lung in the treatment of lung-Qi deficiency have great effects on AR.

Treatment of spleen-Qi deficiency is replenishing Qi to invigorate the spleen. The commonly used prescriptions are decoction of 4 noble, Bu Zhong Yi Qi decoction, Shenling Baizhu decoction, *etc.* Qiu and colleagues<sup>389,390</sup> have shown that the onset of AR is closely related to spleen-Qi deficiency and that Bu Zhong Yi Qi decoction plays a role in the inhibition of cellular infiltration of acidophilic granulocytes and mastocytes in nasal mucosa in experimental spleen-Qi deficiency AR.

Treatment of lung heat is clearing lung-heat and relieving a stuffy nose. Xin Yi Qing Fei Yin is a commonly used prescrip-

tion. Zuwang Gan, a well-known Chinese otorhinolaryngology expert and one of the founders of modern otorhinolaryngology discipline in TCM, proposed that the treatment of lung-heat pattern AR is clearing away heat and desensitization and that Qingre Tuomin Decoction is the effective compound formulae for the pattern.<sup>391</sup> The common Chinese herbs include: folium mori, peppermint, periostracum cicada, earthworm, beautiful sweetgum fruit, radix lithospermi, radix rubiae, Yerbadetajo Herb, *etc.*

Apart from the syndrome differentiation-oriented treatments for AR mentioned above, several randomized controlled clinical trials have investigated the efficacy and safety of Chinese herbal medicine (CHM) in Chinese patients with AR.<sup>392-396</sup> Chan and colleagues<sup>392</sup> reported that the Chinese herbal formulae (Cure-allergic-rhinitis Syrup [CS] and Yu-ping-feng San [YS]) were effective in reducing symptoms and enhancing the quality of life in AR patients with 'yang- and/or Qi-deficiency' body constitution. Similarly, Min and colleagues<sup>393</sup> provided evidence that moxibustion in combination with a Chinese herbal preparation, comprising white mustard seed, euphorbia, corydalis tuber and ginger juice, was significantly more effective than loratadine in reducing symptoms and enhancing the quality of life in patients with AR. Another randomized controlled trial demonstrated that the Chinese herbal formula Shi-Bi-Lin was also significantly more effective than placebo in relieving symptoms of nasal blockage and improving quality of life in patients with PAR.<sup>394</sup> Chui and colleagues<sup>395</sup> compared the efficacy of a Chinese herbal nose drop preparation in patients with PAR and demonstrated that this preparation also significantly improved clinical symptom scores and several quality of life indices compared to placebo. A study by Hsu and colleagues<sup>396</sup> investigated the effect of herbal point-patch treatment in AR patients and showed that acupoint herbal point-patches were an effective treatment for improvement in quality of life in AR. Besides studies in Chinese patients, some randomized trial also assessed the efficacy of CHM in Korean,<sup>397</sup> Australian<sup>398,399,402</sup> and German<sup>400</sup> patients with AR. Although 2 meta-analysis of clinical trials on traditional CHM for the treatment of AR revealed that CHM interventions appeared to have beneficial effects in patients with AR,<sup>321,402</sup> some clinical trials subsequently provided conflicting data for the potential efficacy of CHM for AR<sup>399,402</sup> Particularly when the effect of CHM was assessed in combination with acupuncture for the treatment of SAR. While one study from Germany<sup>400</sup> demonstrated that CHM combined with acupuncture significantly improved both symptoms and quality of life scores in SAR patients compared to acupuncture treatment alone, another study from Australia<sup>402</sup> failed to show any significant differences in symptomatic relief or improvement in quality-of-life scores in SAR patients treated with CHM + acupuncture or acupuncture alone. While it is possible that the differences in the findings between these studies may attributed to a variety of inherent differences, the true potential of CHM as an effec-



**Fig. 14.** Allergen tolerance: changes in cells of allergic inflammation during allergen tolerance. AIT, allergen-specific immunotherapy; Breg, B regulatory cell; Treg, T regulatory cell.

tive therapy for AR needs to be assessed and confirmed by larger well-controlled multicenter trials in well-characterized patients treated for longer periods.

## 8.4 AIT

### 8.4.1 Mechanisms of immunotherapy

AIT represents a sole potentially curative and specific method of allergy treatment. AIT results in the restoration of immune tolerance toward the allergen of interest (Fig. 14). Numerous studies have shown that the mechanisms underlying AIT include desensitization effects (very early phase), modulation of effector cell responses and related antibody isotypes, modulation of migration of inflammatory cells (*e.g.* mast cells, basophils and eosinophils) and release of their mediators, and induction of Treg cells.<sup>403</sup>

The desensitization effect of AIT is similar to rapid desensitization for hypersensitivity reactions to drugs.<sup>403-406</sup> In the very early phase, the suppression of mast cells and basophils might be affected by changes in other immune factors such as Treg cells and specific IgE levels.<sup>407</sup> Following AIT, dendritic cells can induce T cells with a regulatory phenotype and function (Treg 1 [TR1] cells), which secretes IL-10. Such Treg cells inhibit subsequent inflammatory responses that might be important mediators of the beneficial action of AIT.<sup>408-410</sup> Depletion and adoptive transfer of pulmonary plasmacytoid dendritic cells in a mouse model demonstrated that plasmacytoid dendritic cells played a central role in protection against sensitization to allergen and

development of asthma.<sup>411</sup> In addition, several clinical trials have shown that antigen presenting cells (APCs), including B cells, monocytes and macrophages, produce more IL-10 following AIT, which might lead to increased generation of IL-10-secreting TR1-like cells.<sup>412,413</sup>

In allergic diseases, the activity of both allergen-specific IL-10-secreting TR1-like cells and CD4+CD25+ Treg cells is compromised, but can be ameliorated by AIT.<sup>412,414-417</sup> Modulation of T-cell responses to allergen following AIT occurs in several ways. These include 1) increasing the allergen-induced ratio of Th1 cytokines to Th2 cytokines,<sup>418,419</sup> 2) induction of epitope-specific T-cell anergy that can be blocked by neutralization of IL-10,<sup>422</sup> 3) generation of allergen-specific Treg cells that can suppress the responses of effector T cells following delivery of either whole allergen extracts or synthetic peptides that contain or consist of a T-cell epitope,<sup>416,417</sup> and 4) increasing the production of cytokines with regulatory activity. Induction of mRNA that encodes IL-10 and increased production of IL-10 protein have also been reported to occur in both the blood and the tissues following AIT.<sup>404,416,417,421-423</sup>

When exposed to high concentrations of allergens, the levels of allergen-specific IgG4, IgG1 and IgA, but not specific IgE, are increased.<sup>416,424</sup> Allergen-specific IgG was found to prevent immediate allergic skin inflammation following AIT. IgG isotypes could compete with IgE for the same epitopes, resulting in the binding of allergen and were therefore termed blocking antibodies.<sup>425-429</sup> Studies analyzing IgG isotypes induced by AIT have

**Table 10.** Indications for and contraindications to AIT

Indications
Patients with AR/conjunctivitis and/or allergic asthma who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens; includes patients who:
- Do not achieve control of symptoms with avoidance measures and pharmacotherapy
- Do not want ongoing or long-term pharmacotherapy
- Experience undesirable side effects with pharmacotherapy
Contraindications
- Patients on beta-blockers (relative contraindication with venoms)
- Patients with uncontrolled or severe asthma
- Significant co-morbid diseases, such as cardiovascular disability
Special considerations
- Children <5 years of age
- Pregnancy
- The elderly
- Patients with malignancy, immunodeficiency or autoimmune diseases

shown that the concentrations of IgG1 and particularly IgG4 were increased 10- to 100-fold following AIT, influencing the blocking activity on IgE-mediated responses.<sup>430-433</sup>

#### 8.4.2 Indications and contraindications

AIT is indicated in patients with AR/conjunctivitis and/or allergic asthma with the evidence of specific IgE antibodies to clinically relevant allergens<sup>434,435</sup> (Table 10). SPT is the preferred method of testing for specific IgE antibodies. *In vitro* allergen-specific IgE testing is a reasonable alternative to SPT.

##### 1) Contraindications

AIT is contraindicated to patients with the conditions that increase their risk of dying from treatment-related systemic reactions such as severe or poorly controlled asthma, or significant cardiovascular diseases (e.g., unstable angina, recent myocardial infarction, significant arrhythmia and uncontrolled hypertension)<sup>434-436</sup> (Table 10). Patients using beta-blockers are also contraindicated to AIT because these agents can amplify the severity of the reaction and make the treatment of systemic reactions more difficult.

##### 2) Special considerations

Physicians should weigh the risks and benefits of AIT for children less than 5 years of age, since they may have difficulty in complaining about the potential side effects, especially the systemic effects. Generally, AIT is not initiated in pregnant women; however, it can be safely continued in women who have been on treatment prior to becoming pregnant. Other populations needing special consideration include the elderly who have comorbid medical conditions that may increase the risk of experiencing immunotherapy-associated adverse events, patients with

autoimmune disorders, those with immunodeficiency syndromes and those with malignant disease (Table 10).<sup>434,435</sup>

#### 8.4.3 Routes of administration

AIT carries the risk of anaphylactic reactions and should therefore only be prescribed by physicians who are trained in the treatment of allergy and the use of immunotherapy.

##### 1) SCIT

###### a) Location

The injections must be given by trained personnel, in clinical settings, who are equipped to manage any possible systemic adverse reactions or anaphylaxis.<sup>434-436</sup> All patients receiving AIT should generally be observed for at least 30 minutes after injection to ensure proper management of side reactions.<sup>436</sup>

###### b) Allergen vaccines

Allergen vaccines are commercially available for most of the commonly recognized allergens (e.g. house dust mites and grass/tree pollen). Standardized extracts should be utilized whenever possible, since the efficacy and safety of AIT depend on the quality of the allergen extracts.<sup>434,437</sup>

###### c) Treatment phases

Generally, AIT consists of 2 phases: a build-up phase (also known as up-dosing or induction) and a maintenance phase.<sup>434-438</sup> During the build-up phase, the patient receives weekly injections, starting with a very low dose, with gradual increases in dose over the course of 4-5 months. Accelerated schedules, such as cluster/rush immunotherapy and administration of several injections at increasing doses on a single visit, may also be used. During a cluster schedule, multiple injections (usually 2-3) are administered per visit once a week, reaching maintenance in several weeks, e.g. 6 weeks. In a rush protocol, multiple injections are administered on consecutive days, generally reaching maintenance within 1 week. It has been documented that there is no increase in systemic reactions (SRs) and more rapid achievement of symptomatic improvement for the cluster schedule.<sup>437,438</sup> A rush schedule is associated with an increase in SRs sometimes, but can also be well tolerated.<sup>435</sup> During the maintenance phase, the patient receives injections of the maintenance dose every 6 to 8 weeks, usually for a period of 3 years. After that, many patients experience a prolonged, protective effect, and consideration can therefore be given to stopping therapy.

###### d) Maintenance period follow-up

Maintenance immunotherapy follow-ups include assessment of the efficacy of treatment, monitoring of adverse reactions, assessment of patient compliance, and determining whether immunotherapy can be discontinued or if dose/schedule adjustments are required when the patient is exposed to increased al-

ergen levels or when he/she is experiencing an exacerbation of symptoms.<sup>434</sup>

#### e) Efficacy assessment

Symptom and medication scores are generally recommended to assess the clinical efficacy.<sup>434-438</sup> At present, there are no other generally acceptable specific tests or clinical markers that can be used to assess the efficacy. Allergen specific IgG4 and IL-10-secreting type I Treg cells have been measured in some studies and found to be increased gradually.<sup>439</sup>

#### f) Safety

AIT is generally safe and well-tolerated when used in appropriately selected patients.<sup>437,438</sup> However, local and systemic reactions may occur. Local reactions such as wheal, subcutaneous induration and redness/itching at the injection site can generally be managed with local treatment (*e.g.*, cool compresses or topical corticosteroids) or oral antihistamines. Systemic reactions, generally grade 1 or 2, occur in about 1% of injections on AIT. The most severe reaction is anaphylaxis, although fatal anaphylactic reactions are rare.

### 2) Sublingual immunotherapy

#### a) Location

Although sublingual immunotherapy (SLIT) is approved for home use, guidelines indicate that the first 1 or more SLIT doses should be administered in a physician-supervised setting with a 30-minute observation period and thereafter at home.<sup>440</sup>

#### b) Allergen vaccines

There are 2 forms of SLIT preparations—aqueous and tablet.<sup>441</sup> Currently, there is only 1 aqueous formulation for HDM that is used in China.<sup>376</sup>

#### c) Treatment phases

The HDM SLIT vaccine approved by the China Food and Drug Administration is used in the form of drops (No. 1, 1 µg/mL; No. 2, 10 µg/mL; No. 3, 100 µg/mL; No. 4, 333 µg/mL; and No. 5, 1,000 µg/mL). In the up-dosing phase of SLIT, patients are administered with increasing doses starting from No.1 to No.3 during the first 3 weeks. Children (4-14 years old) are maintained with the No.4 and adult (≥ 14 years old) maintained with the No.5. Patients are instructed to keep the drops under the tongue for 1-3 minutes before swallowing. The whole treatment period is 3-5 years.

#### d) Maintenance period follow-up

It is important and necessary to establish a normalized patient management system which includes patient records and patient follow-up information. It can assist the clinician to 1) assess the efficacy of treatment, 2) record the clinical data and scores of the patients, 3) monitor adverse reactions, 4) improve

patient compliance, and 5) determine whether immunotherapy can be discontinued or dose/schedule adjustments are required when the patient is exposed to increased allergen levels or when he/she is experiencing an exacerbation of symptoms.

#### e) Efficacy assessment

SLIT has been established as an evidence-based effective treatment in AR. Meta-analyses confirm its efficacy in reducing both symptoms and medication scores.<sup>442,443</sup> There are also increasing studies which show the efficacy of SLIT in Chinese AR patients.<sup>444-447</sup> These studies have assessed various aspects of SLIT including efficacy, safety, adherence, mechanism, mono- or polysensitized patients, children or adults, and AR or asthma.

#### f) Safety

SLIT has a better safety profile than SCIT. The most common adverse effects are minor local reactions in the mouth and the gastrointestinal tract, with few cases of anaphylaxis, but no fatality. Adherence is more favorable for SLIT, since it is safe, non-invasive and easily taken at home, which is especially well suited for children.<sup>448,449</sup>

### 8.4.4 Adverse reactions and management

#### 1) Classification

The adverse reaction of specific allergen immunotherapy is classified as local reaction (LR) or systemic reaction (SR) according to its range and severity.

SCIT-related LR is defined as swelling, erythema or pruritus around the injection site (Fig. 15), involving 26%-82% of the patients and 0.7%-16% of the shots.<sup>450-453</sup> Chinese researchers have reported 62.9% of injections to be accompanied by LRs.<sup>454</sup> Traditionally, SCIT-related LR can be differentiated as early local or late local reaction depending on whether the reaction happens within 30 minutes after injection.<sup>455</sup> LRs seem to be just little bother or no bother to patients, and 96% of patients indicate that they would not discontinue the treatment because of local reactions.<sup>456</sup>

SLIT-related LR is defined as oral pruritus or swelling, gastro-



**Fig. 15.** SCIT-related local reaction.

intestinal symptoms, dizziness, *etc.* The WAO has classified SLIT-related LRs as mild, moderate, severe, and unknown severity, according to the severity of symptoms, if patients require symptomatic treatment and discontinuation of SLIT is required. Most of the LRs tend to disappear after the initial dose and discontinuation because the side effects are almost always less than 5%.<sup>457</sup> According to Chinese studies, 5.1% patients reported LRs with their treatment<sup>454</sup>; however, the rate appeared to be higher (7%-9.6%) in children with combined allergic rhinitis and asthma syndrome.<sup>458</sup>

SCIT-related SRs can range in severity from mild rhinitis or urticaria symptoms to life-threatening anaphylaxis. According to the WAO SCIT SR grading system, SCIT-related SRs are divided into 5 grades<sup>459</sup> based on the organ involved and severity of the SR. The percentage of SR in conventional schedules is approximately 0.1%-0.2% per injection,<sup>459,460</sup> with fatal anaphylaxis reported at a rate of approximately 1 in 1-2.5 million injections.<sup>279,280,461</sup> A recently completed multicenter study in China reported that SRs occurred in 0.47% of injections and that the occurrence of SRs was significantly higher in children than in adults.<sup>462</sup> Risk factors for anaphylaxis include uncontrolled asthma, previous reactions to allergen immunotherapy, dosing errors, hypersensitivity, use of beta-blockers, dosing during the peak pollen season, inadequate waiting time after injections, epinephrine delayed or not given, and accelerated build-up regimens. Uncontrolled asthma is the most important risk factor therein,<sup>279,280,461,463</sup> thus making assessment of asthma severity especially important for the prevention of anaphylaxis.

Compared to SCIT-related SRs, SLIT-related SRs are rarer and occur at a rate of around 0.056% per dose administered.<sup>464</sup> There is still no confirmed report of SLIT-related fatality.

## 2) Management

Premedication could be effective in decreasing LRs during allergen immunotherapy. Oral antihistamines have been demonstrated to be effective in preventing LRs in cluster<sup>465</sup> and rush regimens,<sup>466</sup> whereas leukotriene antagonists have been shown to be effective in rush protocols.<sup>467</sup> However, routine dose adjustments for LRs are not supported by the current literature.<sup>453</sup>

Most of the SCIT-related SRs appear within 30 minutes after injection, although some SRs are biphasic and could occur during 2-48 hours after the injection is administered.<sup>468</sup> However, the second phase reaction is generally mild and additional epinephrine is unnecessary in most cases. Prompt administration of epinephrine is vital when severe SRs occur<sup>469</sup> as a lot of anaphylaxis-related fatalities are due to the delay of epinephrine use.

The specific management of adverse events is shown below (Table 11).<sup>376,470</sup>

## 8.5 Surgical treatment

Medical therapy is successful in a majority of patients with AR, but there are still a large number of patients who fail medical treatment. The effectiveness of surgical treatment for refractory AR has been demonstrated in several studies.<sup>471-474</sup> There is still no gold standard surgical treatment for intractable AR, but the following rules are suggested: 1) strictly follow indications and contraindications of operations, and 2) select the proper surgical procedures and techniques based on a patient's anatomy, severity of disease and comorbidities.

### 8.5.1 Indications

1) Patients with persistent AR are dissatisfied with medical therapy for at least 2 years which consists of antihistamines,

**Table 11.** The specific management of adverse events resulting from immunotherapy

Grade	Symptoms	Management
Large local reaction	Induration diameter > 4 cm (erythema, pruritus, pseudopodium)	Tourniquet usage; Adrenaline (1 mg/mL) 0.1-0.2 mL sealed injection; Steroids topically; Antihistamine orally (i.m. or i.v. when necessary)
Mild to moderate systemic reaction	Induration diameter > 4 cm (erythema, pruritus, pseudopodium), reaction spreading along lymphatics and blood vessels, with rhinitis, conjunctivitis, asthma or urticaria symptoms	Tourniquet usage; Adrenaline (1 mg/mL) 0.1-0.2 mL sealed injection, repeat when necessary (every 15 min); Venous channel; Steroids topically; Antihistamine i.m.; Beta-2 agonist inhalation or i.v. or s.c.; Aminophylline i.v. when necessary; Steroids i.v.; Check blood pressure and pulse rate
Severe systemic reaction (non life-threatening)	Pruritus of palms and soles, pruritus of scalp, skin flush, urticaria rash, dyspnea, tachypnoea, Hoarseness, abdominal pain, nausea, emesis	Adrenaline (1 mg/mL) 0.3-0.5 mg deeply i.m.; Venous channel; Steroids i.v., repeat when necessary; Antihistamine i.m.; Check blood pressure and pulse rate; Beta-2 agonist when necessary; Aminophylline i.v. when necessary Oxygen; Other symptomatic treatment
Anaphylactic shock	Paleness, skin clamminess, blood pressure decreasing, mental status altering, gatism	Adrenaline (1 mg/mL) 0.5-0.8 mg deeply i.m. or (diluted 0.1 mg/mL) 0.3-0.5 mg i.v. (slowly in fractionated doses) may be repeated after 10-20 min; Place patient in supine position; Venous channel, i.v. line (saline); Vasoactive agents to maintain blood pressure; Steroids i.v. or i.v.gtt; Mechanical ventilation when necessary; Check blood pressure, pulse rate and oxygen saturation; Beta-2 agonist when necessary; Aminophylline i.v. when necessary

For children: Adrenaline (1 mg/mL) 0.01 mg/kg (0.01 mL/kg) i.m. If needed (diluted 0.1 mg/mL) i.v. Antihistamine Clemastine (1 mg/mL) 0.0125-0.025 mg/kg i.m. Corticosteroid methylprednisolone 2 mg/kg i.v.

corticosteroid, leukotriene inhibitors and immunotherapy, and their symptoms significantly impact their quality of life. 2) The physician feels that surgical therapy may significantly improve symptoms and quality of life beyond what medical management has been able to accomplish.<sup>475</sup>

### 8.5.2 Contraindications

1) Patients have not ever been implemented medical therapy or immunotherapy. 2) Symptoms of concurrent asthma are not controlled. 3) Coagulation dysfunction of patients appears to be a tendency for bleeding. 4) Patients with poor health conditions hardly tolerate surgical procedures. 5) Patients with mental illness may be contraindicated to surgical treatment.<sup>376</sup>

### 8.5.3 The main procedures

#### 1) Inferior turbinate reduction surgery

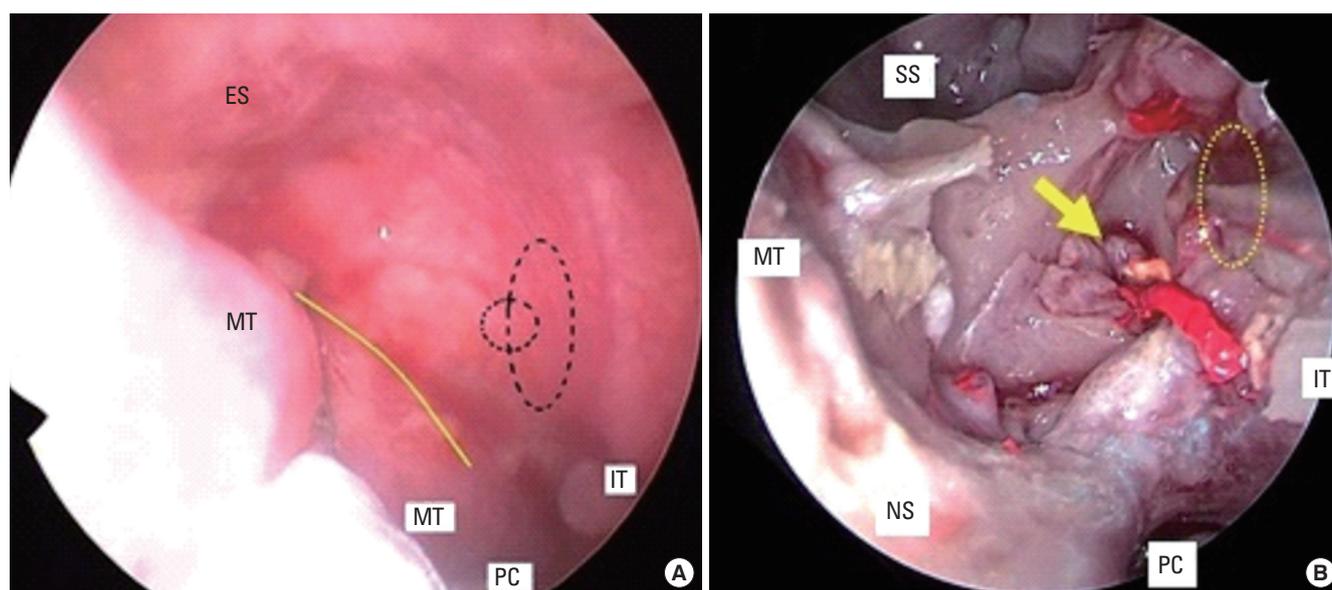
Severe nasal obstruction is a common symptom of AR that is resistance to medical therapy, and it is the most amenable to surgical intervention. Enlargement of the inferior turbinate is the main cause of nasal obstruction in intractable AR. Numerous techniques and procedures have been reported for reducing the volume of the inferior turbinate including submucosal resection, partial turbinectomy, radiofrequency ablation/coagulation, microdebrider and laser turbinoplasty. Septalplasty may be used for patients with severe nasal septum deviation. The improvement rate of nasal obstruction has reported to be 80%-98% 3-12 months after treatment,<sup>476-478</sup> and approximately 50% 3 years after treatment.<sup>479-482</sup>

#### 2) Endoscopic vidian neurectomy

The 4 main symptoms that distress persistent AR patients are associated with dysfunction of the autonomic and sensory nerve imbalance in the nasal mucosa. The mechanism underlying neuronal-immune modulation is related to the symptoms of AR.<sup>483</sup> The inhibition of parasympathetic nerve significantly relieves the symptoms of AR.<sup>484</sup> Golding-Wood<sup>485</sup> first developed transantral vidian neurectomy for treating vasomotor rhinitis and AR, with the transseptal and transpalatal approaches being reported a decade following Golding-Wood's report.<sup>475</sup> However, none of these approaches offer entirely satisfactory outcomes, likely due to difficulties in nerve identification without magnification, risk of significant complications, including the palate fistula and damage to vision, and troublesome bleeding within a small surgical field.<sup>475</sup> Recent advancements in endoscopic techniques of vidian neurectomy have made surgery safer and more effective (Fig. 16). Clinical studies reported that over 90% of patients with refractory AR were satisfied with surgical results during the 12 months follow-up period after endoscopic vidian neurectomy,<sup>486,487</sup> and approximately 65% of patients undergoing bilateral endoscopic vidian neurectomy categorized their symptoms as much improved at the end of the 3 to 6 years follow-up period.<sup>471,482</sup> Temporary dry eyes were reported in 23% to 72.9% of patients, and palatal numbness in 3% to 9%, which were resolved without any special treatment.<sup>471,486,487</sup> No severe complications were noted in the studies.

#### 3) Endoscopic posterior nasal neurectomy

The posterior nasal nerve consists of postganglionic fibers of



**Fig. 16.** Vidian neurectomy diagram. (A) The area of incision and anatomical surroundings of interest in endoscopic vidian neurectomy. Yellow curved line indicates an incision; the oval, the location of sphenopalatine foramen; and the circle, the location of the pterygoid canal. (B) The yellow arrow indicates the horn-shaped pterygoid canal and nerve. E, indicates ethmoid sinus; IT, inferior turbinate; MT, middle turbinate; SS, sphenoid sinus; NS, nasal septum; PC, posterior choana.

pterygoid nerve and maxillary nerve sensory fibers, and it passes through the sphenopalatine foramen into the nasal cavity. Resection of the posterior nasal nerve lowers the hypersensitivity of nasal mucosa and reduces secretion, and alleviates inflammatory reaction.<sup>488</sup> As a modified technique of vidian neurectomy, it has been demonstrated to have satisfactory short-term efficacy in severe allergic rhinitis, without the complication of dry eyes.<sup>473,474,489</sup> However, the long-term efficacy of this procedure has not been noted in the published reports.

## 8.6 Acupuncture

Acupuncture is a traditional form of Chinese medicine, which can be traced back to 2,500 years ago, and more recently it has been widely used as a therapeutic modality for various otolaryngologic disorders.<sup>490,491</sup> The latest American Clinical Practice Guideline for AR published in 2015, recommends that acupuncture be offered as an option for patients with interest in nonpharmacologic approaches to management of AR.<sup>492,493</sup> Several recent international randomized controlled trials have also confirmed the efficacy of acupuncture in the treatment on AR.<sup>492,493</sup>

In conventional acupuncture for nasal inflammatory disease, needles are punctured at specific acupoints (termed Xuewei in Chinese) in the body and gently manipulated until the patient feels “de-qi sensation” (*i.e.* subjective feeling for patients are soreness, numbness heavy or distension, and objective feeling for acupuncturist is heavy and tight feeling under the fingers).

### 8.6.1 Acupuncture therapies on general acupoints to treat AR

Some Chinese acupuncturists have demonstrated that acupuncture works in the treatment of AR and achieves similar efficacy in moderate and severe AR as Western medicine. Acupuncture therapy is the safe and has no apparent adverse reactions.<sup>494</sup> Indeed, a randomized controlled trial comparing the clinical efficacy and safety of acupuncture treatment with Western medicine in patients with moderate and severe persistent AR has recently concluded that acupuncture is not only a safe and effective intervention in these patients, but also the efficacy presents much more advantageous at its durability in the acupuncture group compared to the Western medicine group.<sup>495</sup> An earlier study has also shown that penetration needling at various points has an obvious therapeutic effect on AR, which is even better than oral administration of Biyankang, a patented Chinese herbal medicine formulated for rhinitis.<sup>496</sup> The basic acupoints for AR patients are Fengchi (GB 20), Yingxiang (LI 20), Feishu (BL 13) and Taiyuan (LU 9) for different causative factors.<sup>497</sup> Acupuncture sometimes has a definite therapeutic effect on AR, especially with the anterior and posterior acupoint association method.<sup>498</sup> The possible mechanisms underlying the efficacy of acupuncture treatment in AR are as follows: acupuncture may help improve the blood indices with an increased volume of blood flow and regulate the immunologic function of the human body which bring out therapeutic effects for AR.<sup>497</sup>

There is some evidence that acupuncture treatment can also reduce plasmatic level of IL-10 in chronic AR patients.<sup>499</sup>

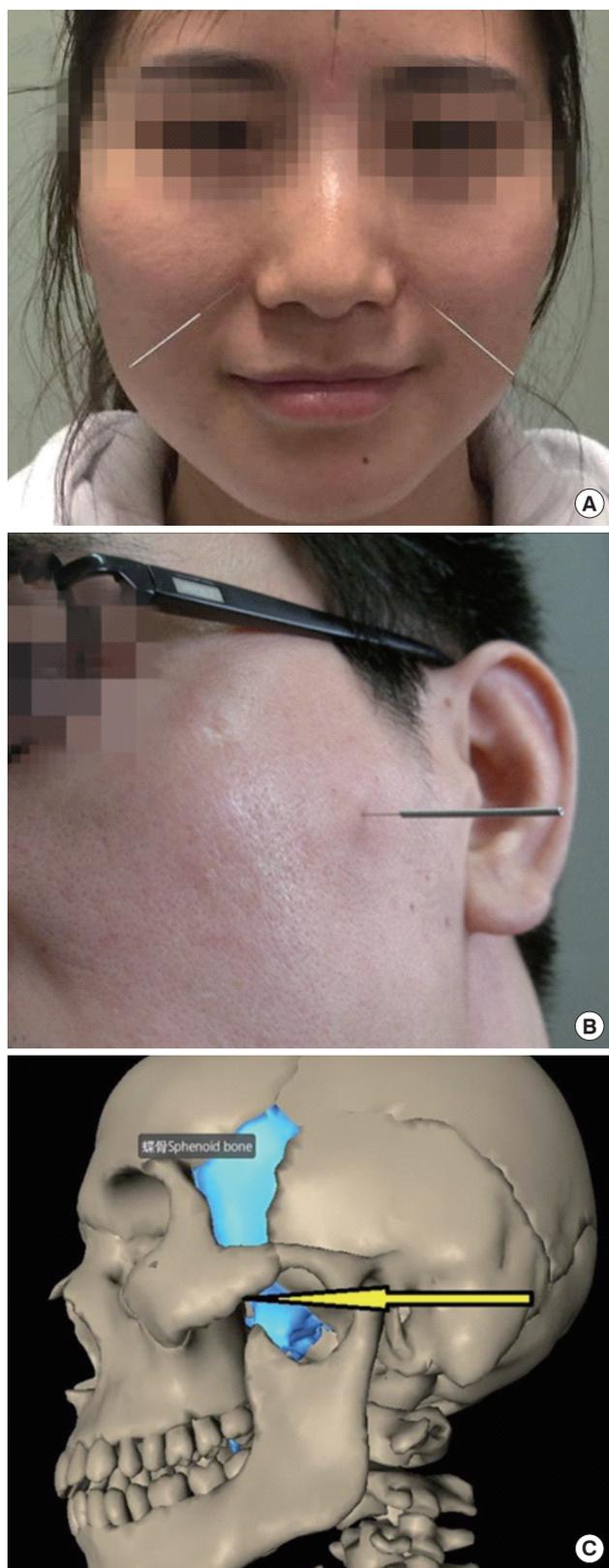
### 8.6.2 Acupuncture therapies on special acupoints to treat AR

Acupuncture at 3 nasal points and the acupoints selected by syndrome differentiation have been shown to achieve a similar short-term efficacy on perennial AR compared to oral administration of loratadine.<sup>500</sup> However, acupuncture therapy appears to be more advantageous for long-term efficacy compared to loratadine. A systematic review has recently indicated acupoint application for AR as follows: acupoints in lung and bladder meridians are mainly selected to assist exterior and resist the pathogenic Qi, and points in spleen and kidney meridians can treat AR fundamentally by joint use.<sup>501</sup> Warm acupuncture in both summer and winter has been shown to improve the QOL of AR patients to a significantly greater extent than cetirizine, and this effect was also accompanied by a significantly greater decrease in serum IgE levels in acupuncture-treated patients, compared to cetirizine-treated patients.<sup>502</sup> Jin's 3-needle therapy achieves superior efficacy on AR of lung-Qi deficiency and cold syndrome than administration of desloratadine oral suspension.<sup>503</sup> The therapy of penetrating needling at head acupoints is safe for patients with PAR, and its effects can be found both in the short and long term.<sup>504</sup> Compared to Western medication, the better efficacy of acupuncture and auricular pressing therapy in improvement of symptoms and signs of AR appear to be achieved by inhibition of the differentiation from Th cells to Th2 cells, adjustment of Th1/Th2 cells imbalance and reduction of IgE synthesis.<sup>505</sup>

In recent years, some acupuncturists have penetrated the needle at one special acupoint to reach the sphenopalatine ganglion (SPG) and get a definite effect (Fig. 17).<sup>506</sup> It was concluded that SPG acupuncture could help improve nasal ventilation by increasing sympathetic nerve excitability in healthy volunteers. Two recent studies have also indicated that stimulation of the SPG by acupuncture can improve nasal symptoms and quality of life in nasal inflammatory diseases.<sup>507,508</sup> Thus, it is possible that acupuncture-stimulated neural regulation may offer an alternative form of therapy for the management of nasal inflammatory disease in the future.

### 8.6.3 Connected therapies on acupoints to treat AR

Application of the dog days plaster at Dazhui (GV 14), Feishu (BL 13), Pishu (BL 20) and Shenshu (BL 23) has been shown to achieve obvious effects with good safety for AR.<sup>509</sup> In the same season, both acupoint sticking therapy in dog days and in non-dog days can improve the symptoms of AR, but the former is better than the latter.<sup>510</sup> Sometimes, dog-days moxibustion could be considered an enhanced method for the prevention and treatment of PAR.<sup>511</sup> A test involving plastered and blistered application of 10% Cantharides extract on Dazhui, Neiguan point has shown that its effectiveness rate was 88%.<sup>512</sup> In particular, nasal



**Fig. 17.** Acupuncture site. (A) Common acupuncture sites. (B) Site of sphenopalatine ganglion acupuncture for AR. (C) High-resolution CT scan 3-dimensional reconstruction of the sphenopalatine ganglion acupuncture site.

allergen provocation test-induced-symptoms were significantly alleviated by the therapy, and there was a significant decrease in both the numbers of eosinophils and basophils in nasal secretion and serum total IgE levels. However, compared to acupoint plaster therapy, triple-strong stimulation therapy at Dazhui (GV 14) has been shown to achieve a superior effect on the prevention and treatment of AR in children, and has a good long-term effect in preventing recurrence.<sup>513</sup> The medicinal vesiculation combined with quick cupping at Shenque (CV 8) has a better effect for AR with syndrome of yang deficiency than oral administration of loratadine and nasal spray of budesonide.<sup>514</sup> Acupoint catgut embedding therapy combined with acupuncture-moxibustion therapy is also safe and effective in the treatment of AR and displays more advantages for the long-term efficacy.<sup>515</sup> However, the effect of catgut implantation needs to be substantiated in high-quality studies and in larger sample sizes in the future.<sup>516</sup> Acupoint autohemotherapy has also been shown to significantly relieve clinical symptoms of AR, and this effect is probably associated with an increase in serum IL-12 content and the promotion of IFN- $\gamma$  synthesis.<sup>517</sup> Point-injection plus TDP radiation is an ideal therapy with a short therapeutic course, with no adverse effect and reliable therapeutic effect for AR.<sup>518</sup>

To sum up, an increasing body of evidence indicates that acupuncture is a safe treatment option, and most of the acupuncture methods employed can improve AR symptoms of nasal itching, sneezing, rhinorrhea, and especially nasal stuffiness. Acupuncture at either general or special acupoints needs to be continued over several weeks to observe significant beneficial and stable effects on symptom improvement. Dog days plaster and acupoint catgut embedding therapy can provide long-term regulation for AR patients. SPG puncturing method is a new and unusual technique, with great potential for development.

### 8.7 Probiotics

The interest in probiotic and its potential benefits in the prevention and treatment of diseases, including allergic diseases, are significantly increasing worldwide. Regrettably, apart from data from a few animal experiments<sup>519,520</sup> and investigations of some other diseases,<sup>521,522</sup> there is relatively little information on the use of probiotics in the treatment of allergic disease in China. Moreover, the available evidence is not strong enough to verify a preventive and therapeutic role of probiotics in allergy,<sup>523</sup> and studies from other parts of the world have provided widely different data,<sup>524</sup> probably due to differences in many aspects of study design, for example, the use of different probiotic strains/combinations and different dosage/timing as well as different demographic and genetic backgrounds. A recent meta-analysis has shown that the use of multistrain probiotics appeared to be most effective for eczema prevention, although no cogent evidence of its preventive effect has been shown for other allergic manifestations.<sup>525</sup> To date, experts have not reached a consensus regarding the recommendation of probiotics for al-

lergy prevention and treatment. There are still needs strong evidence based on adequately powered, well-designed, randomized, controlled trials and a more standardized approaches to support their use before final clinical recommendations on specific strains, dosage and timing can be given.

## 9. CLINICAL OUTCOME ASSESSMENT

Assessments of clinical outcomes of AR should be made both in the short (recent assessment) and long term. The assessments are mainly composed of subjective assessments,<sup>11</sup> which include symptom scores, medication scores and QOL questionnaire of the patients.

### 9.1 Symptom scores

Subjective assessment of symptoms of AR is generally based on scores for 4 nasal symptoms (sneezing, rhinorrhea, nasal itching and nasal obstruction) and 2 ocular symptoms (ocular itching/grittiness/redness and ocular tearing).<sup>276</sup> For patients with concomitant asthma, symptom scores for wheezing, cough, shortness of breath and chest distress are also evaluated.

Four-point scale or VAS is used to quantify the above assessments.<sup>276</sup>

#### 9.1.1 Four-point scale:

- 0: No symptoms
- 1: Mild symptoms (symptoms present but not troublesome)
- 2: Moderate symptoms (troublesome symptoms but tolerable)
- 3: Severe symptoms (intolerable symptoms with impairment of daily activities and/or sleep)

#### 9.1.2 VAS:

Patients grade their symptoms by putting a vertical line on a 0- to 10-cm line representing severity score from 0, 'no symptoms' to 10, 'highest level of symptoms.'

### 9.2 Medication scores

Medication scores are usually used in AR patients that are undergoing AIT or surgical treatment. The assessment should also be reported on a daily basis and scored per day<sup>276</sup> as follows:

- 1: Oral and/or topical H<sub>1</sub>-antihistamines (intranasal or intra-ocular)
- 2: INS
- 3: Oral corticosteroids

When the AR patient also suffers from asthma, the score should also be calculated per day as follows:

- 1:  $\beta_2$ -agonist
- 2: Inhaled corticosteroids

### 9.3 QOL

The authorized Chinese version of RQLQ<sup>327</sup> is suggested for use in the subjective assessment of the QOL in AR patients. Dif-

ferent versions of the RQLQ are available for use according to different ages as follows: (1) adults  $\geq 18$  years: Standard RQLQ<sup>328,331</sup>; (2) 13-17 years: Adolescent RQLQ<sup>329</sup>; and (3) 6-12 years: Pediatric RQLQ.<sup>330</sup>

## 10. PATIENT EDUCATION

Patient education regarding environmental control, pharmacotherapy, immunotherapy and surgical treatment is essential for the management of AR. The education must be carried out based on good communication between physicians and patients. Patients need to know not only what to do, but also why and how to do towards the disease at the outset.

Generally, a stepwise education would help patients realize the characterization of AR and its detrimental effects on QOL, understand the related treatment strategy, and complete physical and emotional preparation for accepting a long-lasting treatment. In this sense, active participation of patients can be helpful in reducing occurrence of adverse reactions and concomitance, save financial cost, and improve QOL.<sup>526</sup>

The implementation of individualized education is as important as personalized treatment. Except for distinct symptoms, results of the examinations, outcomes of the treatment, economic status and life circumstances of each patient still need to be taken into account.<sup>11</sup> Physicians should educate patients in accordance with their own situation, involving the following items: allergen avoidance, medication use, immunotherapy choice and possible treatment outcomes.

More patience and attention need to be offered to patients who cannot understand the therapeutic strategy or those who find it hard to fulfil self-management. Although these patients might have poor educational attainment, heavy economic burden or other reasons, their desirability of relieving symptoms is very strong. Therefore, relevant dissemination requires covering patients' family members in order to get sufficient support and cooperation.

Moreover, it is notable that children with AR are likely to present symptoms with the involvement of the lungs, throat and ears. Meanwhile, QOL impairment often leads to poor-quality sleep and consequent fatigue. More seriously, poor concentration and school performance in children should be given extra concern.<sup>527</sup> Thus, the children and their guardians' education in regard to early diagnosis and careful treatment are crucial to AR control.

On the other hand, popular science knowledge of AR could be disseminated by using traditional and novel media in an easy-to-understand fashion. However, regional disparity caused by the economic development and/or educational level should not be neglected during the implementation process. AR education might be easily acceptable to patients who live in relatively developed cities. Relatively powerful education for both patients and physicians are extremely urgent in rural and poor

regions. Practicable and available methods should be applied according to local conditions such as network education as well as public assistance and government support. Moreover, better communication and close follow-up are important for patients' confidence building and will consequently improve the compliance and outcomes of the therapy.<sup>528</sup>

## 11. PROSPECT

In conclusion, today much research has been done aiming at the epidemiology of AR, the characteristics of genetic inheritance and the mechanism of AR. The diagnosis and treatment system suitable for the Chinese national condition have been established. However, more work is needed in the future.

In the aspect of epidemiology of AR in China, the data we have now obtained are mainly from the big cities. The extensive epidemiologic characteristic of AR for the whole population in China is unknown. With the rapid development of our economy, not only the lifestyle of the Chinese people, but also the degree of industrialization has seen dramatic changes; the distribution of allergens and the prevalence of AR are also in flux. Thus, we need more longitudinal studies about the regional prevalence of AR. On the other hand, studies about regional distribution of allergens should be continued to be performed, with the aim of determining specific allergens in certain regions.

We have made remarkable progress in the process of uncovering the mechanisms of AR and allergy, but there are still many challenging fields, which deserve further studies.

TCM, including herbal TCM and acupuncture, is a precious wealth passed down by ancient physicians and has shown to have a significant clinical effect in the treatment of AR. In spite of this, the Western therapy system occupies a primary position in the treatment of AR in China. Currently, antihistamines and INS are used as the cornerstone of AR therapy. New drugs such as specific agonists, antagonists and biologics represent a new field in AR therapy. However, basic and clinical research about biologic agents is relatively backward in our country.

For AIT, only the standardized dust mite allergen is currently used in China. Production and application of other allergen vaccines are hysteric for the complicated procedure of approval and registration, and some allergen vaccines for immunotherapy, such as pollen, can only be used in a city like Beijing. Thus, the application and registration of new standardized allergen vaccines for the diagnosis and treatment of AR need to be promoted as soon as possible. Genetically engineered vaccines, which are expected to improve the efficacy of immunotherapy and shorten the course of treatment, have recently been investigated by researchers and some of these are at the clinical trials stage. Li and colleagues<sup>529</sup> constructed a recombinant vaccine containing T-cell epitopes derived from *Der p1* and *Der p2* and showed that it effectively alleviated the allergic inflammation of the airways and lungs in experimental mice. The efficacy of some

DNA vaccines was also validated in AR animal models.<sup>530</sup>

The traditional Chinese therapy should be encouraged for the treatment of AR, but faces challenges. Natural herbal medicines have complicated chemical compositions, and the effective constituents are difficult to separate accurately and standardize quantitatively. Further studies are needed to elaborate the effective components of herbal medicine and the mechanism underlying the drug's benefit. Acupuncture also suffers severely from the absence of high-quality clinical research. Integration of traditional Chinese and Western medicine is also an issue that requires much work in the future.

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